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Description

NOVEL PROTEINS AND POLYNUCLEOTIDES ENCODING THEM

BACKGROUND OF THE INVENTION

Within the field of genetic engineering, polynucleotides encoding proteins of interest have been identified and cloned by methods that require a detailed knowledge of the structure and/or function of the polynucleotide or the encoded protein. These methods include hybridization screening, polymerase chain reaction (PCR), and expression cloning.

With the more recent advent of large DNA sequence databases and the accompanying data analysis tools, identification of genes of interest is possible through the analysis of raw sequence data. Databases can be "mined" to locate sequences that resemble (are "homologous to") sequences of known function. Alignment of similar sequences can be used to place novel sequences within families of structurally similar sequences. These analytical tools can be combined with structural information obtained from, for example, X-ray crystallography to predict the higher order structure of a novel polypeptide. These analyses also facilitate prediction of polypeptide function. These recent technological advances have greatly increased the pace of gene discovery.

Genetic engineering has made available a number of genes and proteins of pharmaceutical or other economic importance. Such proteins include, for example, tissue plasminogen activator (t-PA) (U.S. Patent No. 4,766,075), coagulation factor VII (U.S. Patent No. 4,784,950), erythropoietin (U.S. Patent No. 4,703,008), platelet derived growth factor (U.S. Patent No. 4,889,919), and various industrial enzymes (e.g., U.S. Patents Nos. 5,965,384; 5,942,431; and 5,922,586).

Although estimates vary as to the amount of the human genome that has been identified to date, there remains a need in the art for further characterization of the human genome and the proteins encoded thereby. Previously unknown genes and proteins will be useful in the treatment and/or prevention of many human diseases, included diseases that have heretofore been refractory to treatment.

35 SUMMARY OF THE INVENTION

Within one aspect of the invention there is provided an isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as

shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422. Within one embodiment, the isolated polypeptide is from 15 to 2235 amino acid residues in length. Within another embodiment, the at least fifteen contiguous amino acid residues of SEO ID NO:M are operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEO ID NO:423. Within another embodiment, the polypeptide comprises at least 30 contiguous residues of SEQ ID NO:M. Within a further embodiment, the polypeptide comprises at least 47 contiguous residues of SEQ ID NO:M. Within additional embodiments, the polypeptide is selected from the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, and 420; the group consisting of polypeptides of SEQ ID NOS: 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, and 416; or the group consisting of polypeptides of SEQ ID NOS: 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, and 416.

Within a second aspect of the invention there is provided an isolated, mature protein encoded by a polynucleotide sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421. Within certain embodiments, N is 3, 5, 7, 9, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 81, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 135, 137, 139, 155,

157, 161, 163, 165, 167, 173, 177, 179, 185, 201, 203, 205, 207, 209, 223, 229, 231, 233, 235, 239, 241, 249, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 309, 311, 313, 315, 321, 323, 327, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 61, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 335, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, 415, or 419; N is 3, 5, 7, 11, 15, 17, 23, 27, 41, 47, 53, 65, 67, 69, 71, 89, 91, 93, 95, 97, 101, 105, 107, 109, 111, 121, 123, 129, 133, 137, 139, 155, 157, 161, 163, 165, 167, 173, 177, 179, 201, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 261, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 321, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 405, 407, 411, or 415; or N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.

A third aspect of the invention provides isolated polynucleotides encoding the polypeptides disclosed above. Within certain embodiments of the invention the polynucleotides comprise a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer as defined above

Within a fourth aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and a transcription terminator. Within certain embodiments, M is 4, 6, 8, 10, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 82, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 136, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 186, 202, 204, 206, 208, 210, 224, 230, 232, 234, 236, 240, 242, 250, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 310, 312, 314, 316, 322, 324, 328, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42, 48, 54, 62, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 336, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, 416, or 420; M is 4, 6, 8, 12, 16, 18, 24, 28, 42,

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48, 54, 66, 68, 70, 72, 90, 92, 94, 96, 98, 102, 106, 108, 110, 112, 122, 124, 130, 134, 138, 140, 156, 158, 162, 164, 166, 168, 174, 178, 180, 202, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 262, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 322, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 406, 408, 412, or 416; or M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.

A fifth aspect of the invention provides a cultured cell comprising the expression vector disclosed above. The cultured cell can be used, *inter alia*, within a method of producing a polypeptide, the method comprising (a) culturing the cell under conditions whereby the sequence of nucleotides is expressed, and (b) recovering the polypeptide. The invention also provides a polypeptide produced by this method.

Within a sixth aspect of the ivention there is provided an isolated polynucleotide encoding a fusion protein, wherein the fusion protein comprises a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer as defined above, operably linked to a second polypeptide.

Within a seventh aspect of the invention there is provided an expression vector comprising the following operably linked elements: a transcription promoter; a DNA segment encoding a fusion protein as disclosed above; and a transcription terminator. The invention further provides a cultured cell comprising this expression vector, wherein the cell expresses the DNA segment and produces the encoded fusion protein. Also provided is a method of producing a protein comprising culturing the cell under conditions whereby the DNA segment is expressed, and recovering the second polypeptide. Within one embodiment the recovered second polypeptide is joined to a portion of a protein of SEQ ID NO: M, wherein M is an even integer as defined above.

Within a further aspect of the invention there is provided a computer-readable medium encoded with a data structure comprising SEQ ID NO:X, wherein X is an integer from 1 to 422.

Within an additional aspect of the invention there is provided an antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer as defined above.

These and other aspects of the invention will become evident upon reference to the following detailed description of the invention.

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DETAILED DESCRIPTION OF THE INVENTION

Prior to setting forth the invention in detail, it may be helpful to the understanding thereof to define the following terms:

The term "affinity tag" is used herein to denote a polypeptide segment that can be attached to a second polypeptide to provide for purification of the second polypeptide or provide sites for attachment of the second polypeptide to a substrate. In principal, any peptide or protein for which an antibody or other specific binding agent is available can be used as an affinity tag. Affinity tags include a poly-histidine tract. protein A (Nilsson et al., EMBO J. 4:1075, 1985; Nilsson et al., Methods Enzymol. 198:3, 1991), glutathione S transferase (Smith and Johnson, Gene 67:31, 1988), Glu-Glu affinity tag (Grussenmeyer et al., Proc. Natl. Acad. Sci. USA 82:7952-7954, 1985; see SEQ ID NO:423), substance P, Flag[™] peptide (Hopp et al., Biotechnology 6:1204-1210, 1988), maltose binding protein (Kellerman and Ferenci, Methods Enzymol. 90:459-463, 1982; Guan et al., Gene 67:21-30, 1987), streptavidin binding peptide. thioredoxin, ubiquitin, cellulose binding protein, T7 polymerase, immunoglobulin constant domain, or other antigenic epitope or binding domain. See, in general, Ford et al., Protein Expression and Purification 2: 95-107, 1991. Affinity tags can be used individually or in combination. DNAs encoding affinity tags and otehr reagents are available from commercial suppliers (e.g., Pharmacia Biotech, Piscataway, NJ: Eastman Kodak, New Haven, CT; New England Biolabs, Beverly, MA).

The term "allelic variant" is used herein to denote any of two or more alternative forms of a gene occupying the same chromosomal locus. Allelic variation arises naturally through mutation, and may result in phenotypic polymorphism within populations. Gene mutations can be silent (no change in the encoded polypeptide) or may encode polypeptides having altered amino acid sequence. The term allelic variant is also used herein to denote a protein encoded by an allelic variant of a gene.

The terms "amino-terminal" and "carboxyl-terminal" are used herein to denote positions within polypeptides. Where the context allows, these terms are used with reference to a particular sequence or portion of a polypeptide to denote proximity or relative position. For example, a certain sequence positioned carboxyl-terminal to a reference sequence within a polypeptide is located proximal to the carboxyl terminus of the reference sequence, but is not necessarily at the carboxyl terminus of the complete polypeptide.

A "complement" of a polynucleotide molecule is a polynucleotide molecule having a complementary base sequence and reverse orientation as compared to a reference sequence. For example, the sequence 5' ATGCACGGG 3' is complementary to 5' CCCGTGCAT 3'.

"Corresponding to", when used in reference to a nucleotide or amino acid sequence, indicates the position in a second sequence that aligns with the reference position when two sequences are optimally aligned.

The term "degenerate nucleotide sequence" denotes a sequence of nucleotides that includes one or more degenerate codons (as compared to a reference polynucleotide molecule that encodes a polypeptide). Degenerate codons encompass different triplets of nucleotides, but encode the same amino acid residue (i.e., GAU and GAC triplets each encode Asp).

The term "expression vector" is used to denote a DNA molecule, linear or circular, that comprises a segment encoding a polypeptide of interest operably linked to additional segments that provide for its transcription, wherein said segments are arranged in a way that does not exist naturally. Such additional segments include promoter and terminator sequences, and may also include one or more origins of replication, one or more selectable markers, an enhancer, a polyadenylation signal, etc. Expression vectors are generally derived from plasmid or viral DNA, or may contain elements of both.

The term "isolated", when applied to a polynucleotide, denotes that the polynucleotide has been removed from its natural genetic milieu and is thus free of other extraneous or unwanted coding sequences, and is in a form suitable for use within genetically engineered protein production systems. Such isolated molecules are those that are separated from their natural environment and include cDNA and genomic clones. Isolated DNA molecules of the present invention are free of other genes with which they are ordinarily associated, but may include naturally occurring 5' and 3' untranslated regions such as promoters and terminators. The identification of associated regions will be evident to one of ordinary skill in the art (see for example, Dynan and Tijan, *Nature* 316:774-78, 1985).

An "isolated" polypeptide or protein is a polypeptide or protein that is found in a condition other than its native environment, such as apart from blood and animal tissue. In a preferred form, the isolated polypeptide or protein is substantially free of other polypeptides or proteins, particularly other polypeptides or proteins of animal origin. It is preferred to provide the polypeptides or proteins in a highly purified form, i.e. greater than 95% pure, more preferably greater than 99% pure. When used in this context, the term "isolated" does not exclude the presence of the same polypeptide or protein in alternative physical forms, such as dimers or alternatively glycosylated or derivatized forms.

A "mature protein" is a protein that is produced by cellular processing of a primary translation product of a DNA sequence. Such processing may include

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removal of a secretory signal peptide, sometimes in combination with a propeptide. Mature sequences can be predicted from full-length sequences using methods known in the art for predicting cleavage sites. See, for example, von Heijne (Nuc. Acids Res. 14:4683, 1986). The sequence of a mature protein can be determined experimentally by expressing a DNA sequence of interest in a eukaryotic host cell and determining the amino acid sequence of the final product. For proteins lacking secretory peptides, the primary translation product will be the mature protein.

"Operably linked", when referring to DNA segments, indicates that the segments are arranged so that they function in concert for their intended purposes, e.g., transcription initiates in the promoter and proceeds through the coding segment to the terminator. When referring to polypeptides, "operably linked" includes both covalently (e.g., by disulfide bonding) and non-covalently (e.g., by hydrogen bonding, hydrophobic interactions, or salt-bridge interactions) linked sequences, wherein the desired function(s) of the sequences are retained.

The term "ortholog" denotes a polypeptide or protein obtained from one species that is the functional counterpart of a polypeptide or protein from a different species. Sequence differences among orthologs are the result of speciation.

"Paralogs" are distinct but structurally related proteins made by an organism. Paralogs are believed to arise through gene duplication. For example, α -globin, β -globin, and myoglobin are paralogs of each other.

A "polynucleotide" is a single- or double-stranded polymer of deoxyribonucleotide or ribonucleotide bases read from the 5' to the 3' end. Polynucleotides include RNA and DNA, and may be isolated from natural sources, synthesized *in vitro*, or prepared from a combination of natural and synthetic molecules. Sizes of polynucleotides are expressed as base pairs (abbreviated "bp"), nucleotides ("nt"), or kilobases ("kb"). Where the context allows, the latter two terms may describe polynucleotides that are single-stranded or double-stranded. When the term is applied to double-stranded molecules it is used to denote overall length and will be understood to be equivalent to the term "base pairs". It will be recognized by those skilled in the art that the two strands of a double-stranded polynucleotide may differ slightly in length and that the ends thereof may be staggered as a result of enzymatic cleavage; thus all nucleotides within a double-stranded polynucleotide molecule may not be paired. Such unpaired ends will in general not exceed 20 nt in length.

A "polypeptide" is a polymer of amino acid residues joined by peptide bonds, whether produced naturally or synthetically. Polypeptides of less than about 10 amino acid residues are commonly referred to as "peptides".

The term "promoter" is used herein for its art-recognized meaning to denote a portion of a gene containing DNA sequences that provide for the binding of RNA polymerase and initiation of transcription. Promoter sequences are commonly, but not always, found in the 5' non-coding regions of genes.

A "protein" is a macromolecule comprising one or more polypeptide chains. A protein may also comprise non-peptidic components, such as carbohydrate groups. Carbohydrates and other non-peptidic substituents may be added to a protein by the cell in which the protein is produced, and will vary with the type of cell. Proteins are defined herein in terms of their amino acid backbone structures; substituents such as carbohydrate groups are generally not specified, but may be present nonetheless.

A "secretory signal sequence" is a DNA sequence that encodes a polypeptide (a "secretory peptide") that, as a component of a larger polypeptide, directs the larger polypeptide through a secretory pathway of a cell in which it is synthesized. The larger polypeptide is commonly cleaved to remove the secretory peptide during transit through the secretory pathway.

The present invention is based in part upon the discovery of a group of novel, protein-enoding DNA molecules. These DNA molecules and the amino acid sequences that they encode are shown in SEQ ID NO:1 through SEQ ID NO:436.

20 Sequence analysis predicts that each of the encoded proteins includes an aminoterminal secretory peptide. These secretory peptides are shown below in Table 1, wherein residue numbers are in reference to the indicated SEQ ID NO. As will be understood by those skilled in the art, the cleavage sites predicted by conventional models of secretory peptide cleavage (e.g., von Heijne, Nuc. Acids Res. 14:4683, 1986) are not always exact and may vary by as much as ± 5 residues. In addition, cleavage may occur at multiple sites within 5 residues of the indicated position. The mature form of any given protein may thus consists of a plurality of species differing at their amino termini.

Table 1

Protein	SEQ ID NO:	Residues 1-
AFP210015	2	14
AFP170681	4	26
AFP413680	6	28
AFP483037	8	14
AFP230872	10	27
AFP178828	12	14
AFP200134	14	23
AFP195796	16	22
AFP477303	18	18
AFP354334	20	25
AFP250287	22	17
AFP177000	24	26
AFP278176	26	21
AFP202885	28	18
AFP221312	30	23
AFP239757	32	22
AFP226311	34	20
AFP305901	36	20
AFP325549	38	20
AFP81988	40	14
AFP199200	42	20
AFP290395	44	23
AFP212675	46	20
AFP326051	48	17
AFP512441	50	18
AFP55098	52	15
AFP169796	54	21
AFP280706	56	25
AFP383165	58	23
AFP195467	60	26
AFP134225	62	22
AFP261193	64	28
AFP324422	66	28
AFP374312	68	28
AFP258118	70	24
AFP74517	72	25
AFP254653	74	18
AFP108666	76	21
AFP8766	78	15
AFP397185	80	20
AFP195042	82	21
AFP310695	84	26
AFP70022	86	19
AFP121670	88	22
AFP345861	90	15
	70	13

AFP395942	92	16
AFP170291	94	21
AFP297548	96	22
AFP188135	98	28
AFP302388	100	19
AFP263430	102	17
AFP201273	104	18
AFP98983	106	25
AFP581958	108	20
AFP404202	110	19
AFP207203	112	15
AFP220790	114	19
AFP536326	116	23
AFP257473	118	22
AFP248380	120	16
AFP276202	122	20
AFP227568	124	23
AFP229039	126	20
AFP176297	128	_ -
AFP356885	130	17
AFP226938	130	17 16
AFP138504	134	
AFP359196		29
AFP501809	136	24
AFP152733	138	27
AFP541394	140	15
AFP243183	142	23
	144	20
AFP80739	146	18
AFP361806	148	26
AFP483930	150	21
AFP257336	152	25
AFP195800	154	23
AFP179530	156	19
AFP279267	158	14
AFP299766	160	29
AFP244615	162	16
AFP325761	164	22
AFP226024	166	22
AFP257094	168	27
AFP197103	170	27
AFP271855	172	17
AFP324816	174	29
AFP407963	176	25
AFP369635	178	17
AFP93743	180	28
AFP243230	182	15
AFP169316	184	21
AFP130852	186	15

AFP194191	188	22
AFP213472	190	21
AFP360430	192	22
AFP491309	194	21
AFP193428	196	23
AFP366534	198	22
AFP22706	200	27
AFP389012	202	14
AFP137186	204	24
AFP127023	206	21
AFP389687	208	16
AFP293220	210	25
AFP425535	212	25
AFP301494	214	25
AFP345421	216	19
AFP216667	218	26
AFP247951	220	29
AFP4464	222	22
AFP561930	224	28
AFP192851	226	22
AFP252759	228	20
AFP199044	230	20
AFP357958	232	28
AFP117501	234	15
AFP194554	236	23
AFP371069	238	23
AFP313600	240	19
AFP262739	242	18
AFP180730	244	27
AFP287227	246	28
AFP75785	248	26
AFP174843	250	15
AFP250422	252	15
AFP198645	254	17
AFP238111	256	16
AFP460626	258	24
AFP271081	260	14
AFP277752	262	16
AFP291338	264	15
AFP551038	266	22
AFP301579	268	20
AFP266188	270	16
AFP275580	272	28
AFP298054	274	21
AFP348226	276	23
AFP349106	278	23
AFP288248	280	15
AFP436476	282	19
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AFP352125	284	14
AFP62060	286	25
AFP236718	288	21
AFP75775	290	25
AFP407487	292	23
AFP280451	294	27
AFP11675	296	29
AFP348656	298	16
AFP277451	300	19
AFP287436	302	14
AFP116043	304	28
AFP138740	306	26
AFP15192	308	17
AFP169968	310	27
AFP173341	312	23
AFP17588	314	23
AFP176427	316	20
AFP192633	318	14
AFP193013	320	15
AFP193881	322	16
AFP195562	324	16
AFP199922	326	18
AFP204736	328	17
AFP206179	330	27
AFP221877	332	23
AFP222758	334	26
AFP227032	336	24
AFP229269	338	27
AFP232213	340	25
AFP237679	342	21
AFP249599	344	28
AFP275215	346	21
AFP290397	348	26
AFP306591	350	18
AFP310297	352	20
AFP314720	354	19
AFP318671	356	29
AFP323575	358	21
AFP327160	360	20
AFP329002	362	29
AFP345415	364	24
AFP347179	366	24
AFP359138	368	23
AFP365372	370	17
AFP367284	372	23
AFP372822	374	26
AFP374595	376	29
AFP375952	378	. 25
	576	23

WO 01/29221 PCT/US00/29052

	13	
AFP382913	380	17
AFP389184	382	23
AFP404208	384	20
AFP404279	386	29
AFP409112	388	26
AFP413111	390	19
AFP415635	392	15
AFP421092	394	17
AFP436666	396	25
AFP448623	398	19
AFP454192	400	20
AFP49026	402	28
AFP51688	404	28
AFP525341	406	16
AFP545268	408	15
AFP592620	410	22
AFP62197	412	23
AFP68229	414	25
AFP71288	416	15
AFP77851	418	27
AFP81957	420	15
AFP85168	422	27

A secretory peptide of a protein of the present invention can be used to direct the secretion of other proteins of interest from a host cell. Thus, the present invention provides, inter alia, fusions comprising such a secretory peptide of a protein disclosed herein operably linked to another protein of interest. The secretory peptide can be used to direct the secretion of other proteins of interest by joining a polynucleotide sequence encoding it, in the correct reading frame, to the 5' end of a sequence encoding the other protein of interest. Those skilled in the art will recognize that the resulting fused sequence may encode additional residues of a protein of the present invention at the amino terminus of the protein to be secreted. In the extreme case, the fusion may comprise an entire protein of the present invention fused to the amino terminus of a second protein, whereby secretion of the fusion protein is directed by the secretory peptide of the protein of the present invention. It will often be desirable to include a proteolytic cleavage site between the protein of the present invention (or portion thereof) and the other protein of interest. polynucleotide sequences are then introduced into a host cell, which is cultured according to conventional methods. The protein of interest is then recovered from the culture media. Methods for introducing DNA into host cells, culturing the cells, and isolating recombinant proteins are known in the art. Representative methods are summarized below.

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Within certain embodiments of the invention, the protein is selected from those listed in Table 2. Within related embodiments of the invention, the polynucleotide is selected from polynucleotides encoding the proteins listed in Table 2, i.e., for a protein of SEQ ID NO:M, the polynucleotide is SEQ ID NO:M-1.

Table 2

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SEQ ID NO:	Protein	SEQ ID NO:	Protein
6	AFP413680	234	AFP117501
12	AFP178828	236	AFP194554
18	AFP477303	240	AFP313600
24	AFP177000	242	AFP262739
42	AFP199200	252	AFP250422
48	AFP326051	254	AFP198645
66	AFP324422	258	AFP460626
68	AFP374312	270	AFP266188
72	AFP74517	272	AFP275580
90	AFP345861	288	AFP236718
92	AFP395942	294	AFP280451
96	AFP297548	300	AFP277451
98	AFP188135	306	AFP138740
110	AFP404202	324	AFP195562
134	AFP138504	338	AFP229269
138	AFP501809	342	AFP237679
156	AFP179530	344	AFP249599
158	AFP279267	348	AFP290397
162	AFP244615	350	AFP306591
164	AFP325761	366	AFP347179
174	AFP324816	374	AFP372822
180	AFP93743	378	AFP375952
204	AFP137186	386	AFP404279
206	AFP127023	396	AFP436666
210	AFP293220	398	AFP448623
224	AFP561930	408	AFP545268
230	AFP199044	416	AFP71288

Higher order structures of the proteins of the present invention can be predicted by computer analysis using available software (e.g., the Insight II® viewer and homology modeling tools available from MSI, San Diego, CA; and King and Sternberg, *Protein Sci.* 5:2298-310, 1996). In addition, analytical algorithms permit the identification of homologies between newly discovered proteins and known proteins. Such homologies are indicative of related biological functions.

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AFP254653 is 49% identical in sequence to human lysozyme C. Lysozyme C is a secreted bacteriolytic enzyme with similarity to the alphalactalbumins. Both are small alpha + beta proteins with six conserved cysteines forming a disulfide core comprising three disulfide bonds. AFP254653 may also exhibit bacteriolytic or other antimicrobial activity.

AFP581958 is 43% identical to wheat aluminum-induced protein, a member of the Bowman-Birk proteinase inhibitor family. All serine proteinases possess an exposed inhibitor loop that is stabilized by intermolecular interactions (usually disulfide bonds) between residues flanking the binding loop and the protein core. Interaction between inhibitor and enzyme produces a stable complex that disassociates very slowly, producing either an unaffected or a modified inhibitor that is cleaved at the scissile bond of the binding loop. AFP581958 may be a secreted serine proteinase.

AFP220790 is 42% identical to chicken lysozyme G, a bacteriolytic glycosyl hydrolase that hydrolizes peptidoglycan homopolymers of the prokaryote cell walls. AFP220790 may thus be a secreted bacteriolytic enzyme, and may exhibit other antimicrobial activity.

AFP271855 is 37% identical to bovine granulocyte peptide A precursor (antimicrobial BGP-A). Bovine and murine granulocyte peptide A precursor (also called antimicrobial BGP-A) are disclosed in WIPO publication WO 97/29765. Bovine GP-A was isolated from a bone marrow library (WO 97/29765). GP-A exhibits activity against Gram-positive and Gram-negative bacteria, fungi and viruses. AFP271855 may exhibit antimicrobial (including one or more of anti-bacterial, anti-fungal, and anti-viral) activity.

AFP298054 is 24% identical to human T1/ST2 ligand. The T1 gene is also known as ST2, DER4, and Fit-1. It encodes a member of the interleukin-1 (IL-1) receptor family. It is transcribed in two forms, a soluble form and a membrane-bound form. The classical IL-1 ligands (IL-1α, IL-1β, and IL-1ra) do not bind T1. A putative ligand for T1 was disclosed in 1996 (Gayle et al., *J. Biol. Chem.* 227:5784-5789, 1996). This protein binds T1 but is unable to initiate signal transduction by the membrane-bound form. The ligand is apparently a type I membrane protein. It has a predicted molecular weight (excluding the signal sequence and transmembrane domain) of about 22 kD, and has no sequence or hydrophobicity profile similarity to the beta-trefoil cytokines IL-1 or the FGFs. AFP298054 may be an antagonist that binds the receptor and regulates the activity of an as yet undiscovered IL-1 homolog.

Table 3 lists homologies between AFP sequences and sequences contained in the GenBank database, Derwent protein (PSP) or polynucleotide (PSN) databases, or Protein Identification Resource (PIR).

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Table 3

Accession Number & Description AFP130852 AE003823 (fly genomic) AFP169968 AE003515 (fly genomic) AFP174843 AF283518 (Mus musculus elongation factor sec) AFP176427 AE003808 (fly genomic) AFP178828 PSN_V61483 AFP179530 AE003708 (fly genomic) AFP188135 AE003677 (fly genomic) AFP195042 PIR_T41241 (yeast oxysterol-binding protein family) AFP198645 AE003718 (fly genomic) AFP199200 AF113691 (human clone FLB4739 PRO1238 mRNA) AFP204736 AC069237 (human chromosome 3 clone RP11-175M9) AFP229269 AF247177 (Mus musculus sphingosine-1-phosphate phosphohydrolase) AFP230872 AF150741 (Rattus norvegicus prolactin-like protein J mRNA) AFP279267 AE003559 (fly genomic) AFP347179 AE003499 (fly genomic) Z1041035F6P AFP357958 AF283518 (Mus musculus elongation factor sec mRNA) AFP359196 AE003530 (fly genomic) AFP374312 AE003538 (fly genomic) AFP374312 AE003538 (fly genomic) AFP389687 AE003831 (fly genomic) AFP395942 AB041564 (mouse brain cDNA; clone MNCb-0914) AFP404202 AL137255 (human mRNA; cDNA DKFZp434B1813) AFP413680 X14971 (mouse mRNA for alpha-adaptin, MMADAPA1) AFP477303 AE003778 (fly genomic) AFP477303 AE003778 (fly genomic) AFP62060 PSP_Y94938 (Human secreted protein clone ye78_1) AFP71288 AL161655 (human chromosome 20 clone RP11-116E13) AFP74517 PIR_T16263 (C. elegans hypothetical protein F35D11.3)	Υ	Table 3
AFP169968 AE003515 (fly genomic) AFP174843 AF283518 (Mus musculus elongation factor sec) AFP176427 AE003808 (fly genomic) AFP178828 PSN_V61483 AFP179530 AE003708 (fly genomic) AFP188135 AE003677 (fly genomic) AFP195042 PIR_T41241 (yeast oxysterol-binding protein family) AFP198645 AE003718 (fly genomic) AFP199200 AF113691 (human clone FLB4739 PRO1238 mRNA) AFP204736 AC069237 (human chromosome 3 clone RP11-175M9) AFP229269 AF247177 (Mus musculus sphingosine-1-phosphate phosphohydrolase) AFP230872 AF150741 (Rattus norvegicus prolactin-like protein J mRNA) AFP279267 AE003559 (fly genomic) AFP347179 AE003499 (fly genomic) Z1041035F6P AFP357958 AF283518 (Mus musculus elongation factor sec mRNA) AFP359196 AE003530 (fly genomic) AFP389687 AE003538 (fly genomic) AFP389687 AE003831 (fly genomic) AFP404202 AL137255 (human mRNA; cDNA DKFZp434B1813) AFP413680 X14971 (mouse mRNA for alpha-adaptin, MMADAPA1) AFP47208 AL161655 (human chromosome 20	Locus	Accession Number & Description
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AFP374312 AE003538 (fly genomic) AFP389687 AE003831 (fly genomic) AFP395942 AB041564 (mouse brain cDNA; clone MNCb-0914) AFP404202 AL137255 (human mRNA; cDNA DKFZp434B1813) AFP413680 X14971 (mouse mRNA for alpha-adaptin, MMADAPA1) AFP477303 AE003778 (fly genomic) AFP62060 PSP_Y94938 (Human secreted protein clone ye78_1) AFP71288 AL161655 (human chromosome 20 clone RP11-116E13)	AFP357958	AF283518 (Mus musculus elongation factor sec mRNA)
AFP389687 AE003831 (fly genomic) AFP395942 AB041564 (mouse brain cDNA; clone MNCb-0914) AFP404202 AL137255 (human mRNA; cDNA DKFZp434B1813) AFP413680 X14971 (mouse mRNA for alpha-adaptin, MMADAPA1) AFP477303 AE003778 (fly genomic) AFP62060 PSP_Y94938 (Human secreted protein clone ye78_1) AFP71288 AL161655 (human chromosome 20 clone RP11-116E13)	AFP359196	
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AFP477303 AE003778 (fly genomic) AFP62060 PSP_Y94938 (Human secreted protein clone ye78_1) AFP71288 AL161655 (human chromosome 20 clone RP11-116E13)	AFP404202	AL137255 (human mRNA; cDNA DKFZp434B1813)
AFP477303 AE003778 (fly genomic) AFP62060 PSP_Y94938 (Human secreted protein clone ye78_1) AFP71288 AL161655 (human chromosome 20 clone RP11-116E13)	AFP413680	X14971 (mouse mRNA for alpha-adaptin, MMADAPA1)
AFP71288 AL161655 (human chromosome 20 clone RP11-116E13)	AFP477303	
AFP71288 AL161655 (human chromosome 20 clone RP11-116E13)		PSP_Y94938 (Human secreted protein clone ye78_1)
	AFP71288	
	AFP74517	

Table 4 lists AFP proteins for which regions of identity have been found in the GenBank database.

Table 4

1 dole 4		
Locus	Accession Number & Description	
AFP127023	SK000740 (human cDNA FLJ20733; clone HEP08550; by homology: molybdopterin cofactor sulfurase)	
AFP134225	AB020970 (human mRNA; partial cds and 3'UTR; up-regulated by BCG-CWS)	
AFP195562	AK000382 (human cDNA FLJ20375; clone HUV00942)	

AFP199044	HSU80813 (human nucleoside diphosphate kinase homolog DR-nm23)
AFP227032	AK001848 (human cDNA FLJ10986; clone PLACE1001869; weakly
	similar to L-RIBULOKINASE; EC 2.7.1.16)
AFP237679	AB000465 (human mRNA; exon 1; 2; 3; 4; clone:RES4-24B; in
	genomic region of Huntington's disease locus)
AFP262739	AK000135 (human cDNA FLJ20128; clone COL06181)
AFP369635	PSN_Z24827 (Human secreted protein gene 17 clone HNFIY77)
AFP81957	AF267730 (human 26S proteasome-associated UCH interacting protein 1; UIP1)
AFP93743	AK000066 (human cDNA FLJ20059; clone COL01349)

Table 5 lists AFP proteins for which longer regions of identity have been found in proteins contained in GenBank and other databases.

Table 5

	. Table 3
Locus	Accession Number & Description
AFP117501	AK000505 (human cDNA FLJ20498; clone KAT08960)
AFP138740	HSM802370 (human mRNA; cDNA DKFZp434M1511)
AFP170291	AK000494 (human cDNA FLJ20487; clone KAT08245)
AFP170681	AK001698 (human cDNA FLJ10836; clone NT2RP4001228 close
	paralogue of human Kelch-like 1 protein (KLHL1) mRNA: AF252283)
AFP177000	AK000524 (human cDNA FLJ20517; clone KAT10235)
AFP193881	AK000382 (human cDNA FLJ20375; clone HUV00942)
AFP195796	AF251041 (human SGC32445 protein (SGC32445) mRNA; homology
-	to PSP_W35393 Human TB2 gene product)
AFP202885	AB037808 (human mRNA for KIAA1387 protein)
AFP207203	AF250924 (human PNGase mRNA: peptide N-glycanase)
AFP226024	AK001952 (human cDNA FLJ11090; clone PLACE1005308)
AFP227568	AB019038 (human HMT-1 mRNA for beta-1;4 mannosyltransferase)
AFP244615	AK001009 (human cDNA FLJ10147; clone HEMBA1003369; weak
	homology: CENE_HUMAN CENTROMERIC PROTEIN E)
AFP250422	AF208849 (human BM-007 mRNA)
AFP266188	AK000272 (human cDNA FLJ20265; clone COLF9334; homology to
	major facilitator protein homolog, fission yeast: PIR_S62432)
AFP277451	AK001373 (human cDNA FLJ10511; clone NT2RP2000656)
AFP277752	AK000453 (human cDNA FLJ20446; clone KAT05231; weak
	homology to dinitrogenase reductase activating glycohydrolase (draG)
	Archaeoglobus fulgidus: PIR_C69465)
AFP280451	AL133355 (Human DNA sequence from clone RP11-541N10 on
	chromosome 10. Contains a novel gene and the 5' end of the gene for a
	novel protein; ortholog of mouse FISH protein)
AFP293220	AK001441 (human cDNA FLJ10579; clone NT2RP2003446)
AFP297548	AK000494 (human cDNA FLJ20487; clone KAT08245)
AFP306591	AL359700 (human chromosome 6 clone RP11-802L12)
AFP324816	AB032966 (human mRNA for KIAA1140 protein weak homology:
	Human O-linked GlcNAc transferase mRNA)

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AFP356885	AK001544 (human cDNA FLJ10682; clone NT2RP3000072)
AFP389012	AK000428 (human cDNA FLJ20421; clone KAT02467; homologus to
	human bisphosphate 3'-nucleotidase mRNA: AF125042)
AFP436666	AK001608 (human cDNA FLJ10746; clone NT2RP3001679; likely
l	human orthologue of Rattus norvegicus small rec (srec) mRNA:
	AF228917)
AFP501809	AK001963 (human cDNA FLJ11101; clone PLACE1005623)
AFP525341	AF189692 (human non-kinase Cdc42 effector protein SPEC2 mRNA)

A protein of the present invention can be prepared as a fusion protein by joining it to a second polypeptide or a plurality of additional polypeptides. Suitable second polypeptides include amino- or carboxyl-terminal extensions, such as linker peptides of up to about 20-25 residues and extensions that facilitate purification (affinity tags) as disclosed above. A protein of interest can be prepared as a fusion to a dimerizing protein as disclosed in U.S. Patents Nos. 5,155,027 and 5,567,584. Preferred dimerizing proteins in this regard include immunoglobulin constant region domains. Immunoglobulin-polypeptide fusions can be expressed in genetically engineered cells to produce a variety of multimeric analogs of a protein of interest. Fusion proteins can also comprise auxiliary domains that target the protein of interest to specific cells, tissues, or macromolecules (e.g., collagen). For example, a protein of interest can be targeted to a predetermined cell type by fusing it to a ligand that specifically binds to a receptor on the surface of a target cell. In this way, proteins can be targeted for therapeutic or diagnostic purposes. A protein can be fused to two or more moieties, such as an affinity tag for purification and a targeting domain. Protein fusions can also comprise one or more cleavage sites, particularly between domains. See, Tuan et al., Connective Tissue Research 34:1-9, 1996. Proteins of the present invention can also be used as targetting moieties within fusion proteins comprising, for example, cytokines, cytotoxins, or other biologically active polypeptide moieties.

Protein fusions of the present invention will usually contain not more than about 1,200 amino acid residues joined to the AFP protein. For example, an AFP protein can be fused to *E. coli* β -galactosidase (1,021 residues; see Casadaban et al., *J. Bacteriol.* 143:971-980, 1980), a 10-residue spacer, and a 4-residue factor Xa cleavage site. Such a protein comprising, for example, AFP345421 (SEQ ID NO:216), contains 2235 amino acid residues. In a second example, an AFP protein can be fused to maltose binding protein (approximately 370 residues), a 4-residue cleavage site, and a 6-residue polyhistidine tag.

As disclosed above, the proteins of the present invention or portions thereof can also be used to direct the secretion of a second protein. When such fusions

are designed so that the secreted protein retains a portion of the protein of the present invention, the fusion protein can be purified by means that exploit the properties of the protein of the present invention. Typical of such methods is immunoaffinity chromatography using an antibody directed against a protein of the present invention. When such a fusion is engineered to contain a cleavage site at the fusion point, the fusion can be cleaved and the protein of interest recovered free of extraneous sequence.

The present invention also provides polynucleotide molecules, including DNA and RNA molecules, that encode the proteins disclosed above. Those skilled in the art will readily recognize that, in view of the degeneracy of the genetic code, considerable sequence variation is possible among these polynucleotide molecules. The amino acid sequence information provided herein can be used by one of ordinary skill in the art to generate degenerate sequences comprising all nucleotide sequences encoding a particular polypeptide. Table 6 sets forth the one-letter codes used to denote degenerate nucleotide positions. "Resolutions" are the nucleotides denoted by a code letter. "Complement" indicates the code for the complementary nucleotide(s). For example, the code Y denotes either C or T, and its complement R denotes A or G, A being complementary to T, and G being complementary to C.

TABLE 6

Nucleotide Resolutions Complement Resolutions T T A A C \mathbf{C} G \mathbf{G} G G \mathbf{C} \mathbf{C} T T Α Α A|GR Y CT Y C|TR AG A|CM K G|TK G|TM A|C S C|GS CG W A|TW A|TA|C|T H D A|G|T В C|G|T V A|C|G V ACG C|G|T В A|G|T D A|C|T H N A|C|G|T N A|C|G|T

Degenerate codons encompassing all possible codons for a given amino acid are set forth in Table 7, below.

TABLE 7

Amino	One-Letter		Degenerate
Acid	Code	Codons	Codon
Cys	С	TGC TGT	TGY
Ser	S	AGC AGT TCA TCC TCG TCT	WSN
Thr	T	ACA ACC ACG ACT	CAN
Pro	P	CCA CCC CCG CCT	CCN
Ala	Α	GCA GCC GCG GCT	GCN
Gly	G	GGA GGC GGG GGT	GGN
Asn	N	AAC AAT	AAY
Asp	D	GAC GAT	GAY
Glu	E	GAA GAG	GAR
Gln	Q	CAA CAG	CAR
His	H	CAC CAT	CAY
Arg	R	AGA AGG CGA CGC CGG CGT	MGN
Lys	K	AAA AAG	AAR
Met	M	ATG	ATG
Ile	I	ATA ATC ATT	ATH
Leu	L	CTA CTC CTG CTT TTA TTG	YTN
Val	V	GTA GTC GTG GTT	GTN
Phe	F	TTC TTT	TTY
Tyr	Y	TAC TAT	TAY
Trp	W	TGG	TGG
Ter	•	TAA TAG TGA	TRR
Asn Asp	В		RAY
Glu Gln	Z		SAR
Any	X		NNN
Gap	~		

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One of ordinary skill in the art will appreciate that some ambiguity is introduced in determining a degenerate codon, representative of all possible codons encoding each amino acid. For example, the degenerate codon for serine (WSN) can, in some circumstances, encode arginine (AGR), and the degenerate codon for arginine (MGN) can, in some circumstances, encode serine (AGY). A similar relationship

exists between codons encoding phenylalanine and leucine. Thus, some polynucleotides encompassed by the degenerate sequences may encode variant amino acid sequences, but one of ordinary skill in the art can easily identify such variant sequences by reference to the amino acid sequences disclosed in the accompanying Sequence Listing.

Methods for preparing DNA and RNA are well known in the art. Complementary DNA (cDNA) clones are prepared from RNA that is isolated from a tissue or cell that produces large amounts of the cognate mRNA. Such tissues and cells are identified by methods commonly known in the art, such as Northern blotting (Thomas, *Proc. Natl. Acad. Sci. USA* 77:5201, 1980). Databases of expressed sequence tags (ESTs) can be analyzed to produce an "electronic Northern" wherein sequences are assigned to specific cell or tissue sources on the basis of their abundance within libraries. Table 8, below, shows the results of such an analysis when, as the minimum significant abundance, it was required that at least 10% of all sequences for a given protein were from a single source and at least five individual clones had been identified from that source. Sequences shown in the accompanying Sequence Listing but not listed in Table 8 were widely distributed among various tissues or were represented by few clones.

Table 8

AFP152733	K562 cells
AFP169796	T-cells
AFP173341	testis
AFP17588	fetal liver or spleen
AFP194554	fetal liver or spleen
AFP199922	testis
AFP229269	placenta
AFP237679	fetal liver or spleen
AFP257094	adult brain
AFP258118	epidermal breast keratinocytes
AFP263430	breast
AFP276202	infant brain
AFP287436	testis
AFP290397	testis
AFP306591	fetal heart
AFP325761	K562 cells
AFP352125	testis
AFP359138	infant brain
AFP369635	germinal center B-cells
AFP409112	kidney
AFP483037	neonatal keratinocytes
AFP49026	peripheral blood eosinophils of asthma patients
AFP545268	K562 cells
AFP561930	fetal liver or spleen
AFP62060	testis
AFP62197	pregnant uterus
AFP93743	germinal center B-cells
AFP98983	fetal heart

A panel of cDNAs from human tissues was screened for AFP expression using PCR. The panel was made from first strand cDNAs obtained from Clontech laboratories, Inc., Palo Alto, CA and contained 20 first-strand cDNA samples from the human tissues shown in Table 9. The panel was set up in a 96-well format that further included a human genomic DNA (obtained from Clontech Laboratories, Inc.) positive control sample and a water-only well as a negative control sample. Each well contained approximately 0.2-100 pg/μl of cDNA, diluted with water to 17.5μl. The

PCR reactions were set up by adding oligonucleotide primers, DNA polymerase (Ex TaqTM; TAKARA Shuzo Co. Ltd. Biomedicals Group, Japan or AdvantageTM 2 cDNA polymerase mix; Clontech Laboratories, Inc.) with the appropriate supplied buffer, dNTP mix (TAKARA Shuzo Co. Ltd.), and a density increasing agent and tracking dye (RediLoad; Research Genetics, Inc., Huntsville, AL) to each sample on the panel. The amplification was carried out as follows: incubation at 94°C for 2 minutes; 35 cycles of 94°C for 30 seconds, 60°C for 20 seconds, and 72°C for 30 seconds; followed by incubation at 72°C for 5 minutes. About 10 μl of the PCR reaction product was subjected to standard agarose gel electrophoresis using a 4% agarose gel.

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Total RNA can be prepared using guanidine HCl extraction followed by isolation by centrifugation in a CsCl gradient (Chirgwin et al., *Biochemistry* 18:52-94, 1979). Poly (A)+ RNA is prepared from total RNA using the method of Aviv and Leder (*Proc. Natl. Acad. Sci. USA* 69:1408-1412, 1972). Complementary DNA (cDNA) is prepared from poly(A)+ RNA using known methods. In the alternative, genomic DNA can be isolated. For some applications (e.g., expression in transgenic animals) it may be preferable to use a genomic clone, or to modify a cDNA clone to include at least one genomic intron. Methods for identifying and isolating cDNA and genomic clones are well known and within the level of ordinary skill in the art, and include the use of the sequences disclosed herein, sequences complementary thereto, or parts thereof, for probing or priming a library. Such methods include, for example, hybridization or polymerase chain reaction ("PCR", Mullis, U.S. Patent 4,683,202). Expression libraries can be probed with antibodies to a protein of interest, receptor fragments, or other specific binding partners.

The polynucleotides of the present invention can also be prepared by automated synthesis. Synthesis of polynucleotides is within the level of ordinary skill in the art, and suitable equipment and reagents are available from commercial suppliers. See, in general, Glick and Pasternak, Molecular Biotechnology, Principles & Applications of Recombinant DNA, ASM Press, Washington, D.C., 1994; Itakura et al., Ann. Rev. Biochem. 53: 323-56, 1984; and Climie et al., Proc. Natl. Acad. Sci. USA 87:633-7, 1990.

The present invention further provides antisense polynucleotides that are complementary to a segment of a polynucleotide as set forth in one of SEQ ID NO:N, wherein N is an odd integer from 1 to 435. Such antisense polynucleotides are designed to bind to the corresponding mRNA and inhibit its translation. Antisense polynucleotides are used to inhibit gene expression in cell culture or in a patient, and can be used as probes or primers for research or diagnostic purposes.

Probes and primers of the present invention comprise a suitable fragment, and may comprise up to the complete sequence, of a polynucleotide as shown in SEQ ID NO:N or the complement thereof, wherein N is an odd integer from 1 to 421. Probes will generally be at least 20 nucleotides in length, although somewhat shorter probes (14-17 nucleotides) can be used. PCR primers are at least 5 nucleotides in length, preferably 15 or more nt, more preferably 20-30 nt. Shorter polynucleotide probes and primers are referred to in the art as "oligonucleotides," and can be DNA or RNA. Probes will generally comprise an oligonucleotide linked to a label, such as a radionuclide.

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Probes and primers as disclosed herein can be used for cloning allelic, orthologous, and paralogous sequences. Allelic variants of the disclosed sequences can be cloned by probing cDNA or genomic libraries from different individuals according to standard procedures. Orthologous sequences can be cloned using information and compositions provided by the present invention in combination with conventional cloning techniques. For example, a cDNA can be cloned using mRNA obtained from a tissue or cell type that expresses the protein. Suitable sources of mRNA can be identified by probing Northern blots with probes designed from the sequences disclosed herein. A library is then prepared from mRNA of a positive tissue or cell line. A cDNA can then be isolated by a variety of methods, such as by probing with a complete or partial human cDNA or with one or more sets of degenerate probes based on the disclosed sequences. A cDNA can also be cloned by PCR using primers designed from the sequences disclosed herein. Within an additional method, the cDNA library can be used to transform or transfect host cells, and expression of the cDNA of interest can be detected with an antibody to the encoded protein. Similar techniques can also be applied to the isolation of genomic clones. Orthologous and paralogous sequences can be identified from libraries by probing blots at low stringency and washing the blots at successively higher stringency until background is suitably reduced.

Probes and primers disclosed herein can be used to clone 5' non-coding regions of a corresponding gene. In view of the tissue-specific expression observed for certain proteins of the invention (Tables 8 and 9), promoters of these genes are expected to provide tissue-specific expression. Such promoter elements can thus be used to direct the tissue-specific expression of heterologous genes in, for example, transgenic animals or patients treated with gene therapy. Cloning of 5' flanking sequences also facilitates production of a protein of interest by "gene activation" as disclosed in U.S. Patent No. 5,641,670. Briefly, expression of an endogenous gene in a cell is altered by introducing into its locus a DNA construct comprising at least a targeting sequence, a regulatory sequence, an exon, and an unpaired splice donor site. The targeting sequence is a 5' non-coding sequence that permits homologous recombination of the construct with the endogenous locus, whereby the sequences within the construct become operably linked with the endogenous coding sequence. In this way, an endogenous promoter can be replaced or supplemented with other regulatory sequences to provide enhanced, tissue-specific, or otherwise regulated expression.

The polynucleotides of the present invention further include polynucleotides encoding the fusion proteins, including signal peptide fusions, disclosed above.

The present invention further provides a computer-readable medium encoded with a data structure that provides at least one of SEQ ID NO:1 through SEQ ID NO:436. Suitable forms of computer-readable media include magnetic media and optically-readable media. Examples of magnetic media include a hard or fixed drive, a random access memory (RAM) chip, a floppy disk, digital linear tape (DLT), a disk cache, and a ZIP® disk. Optically readable media are exemplified by compact discs (e.g., CD-read only memory (ROM), CD-rewritable (RW), and CD-recordable),digital versatile/video discs (DVD) (e.g., DVD-ROM, DVD-RAM, and DVD+RW), and carrier waves.

The polypeptides of the present invention, including full-length proteins, biologically active fragments, immunogenic fragments, and fusion proteins, can be produced in genetically engineered host cells according to conventional techniques. Suitable host cells are those cell types that can be transformed or transfected with exogenous DNA and grown in culture, and include bacteria, fungal cells, and cultured higher eukaryotic cells. Eukaryotic cells, particularly cultured cells of multicellular organisms, are generally preferred for the production of proteins having higher eukaryotic-type post-translational modifications (e.g., γ-carboxylation) and for making proteins, especially secretory proteins, for pharmaceutical use in humans. Techniques for manipulating cloned DNA molecules and introducing exogenous DNA into a variety of host cells are disclosed by Sambrook et al., *Molecular Cloning: A Laboratory Manual*, 2nd ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989, and Ausubel et al., eds., *Current Protocols in Molecular Biology*, Green and Wiley and Sons, NY, 1993.

In general, a DNA sequence encoding a polypeptide of interest is operably linked to other genetic elements required for its expression, generally including a transcription promoter and terminator, within an expression vector. The vector will also commonly contain one or more selectable markers and one or more origins of replication, although those skilled in the art will recognize that within certain systems selectable markers can be provided on separate vectors, and replication of the exogenous DNA can be achieved through integration into the host cell genome. Selection of promoters, terminators, selectable markers, vectors and other elements is a matter of routine design within the level of ordinary skill in the art. Many such elements are described in the literature and are available through commercial suppliers.

To direct a polypeptide into the secretory pathway of a host cell, a secretory signal sequence (also known as a leader sequence, prepro sequence or pre sequence) is provided in the expression vector. The secretory signal sequence may be that of the protein of interest, or may be derived from another secreted protein (e.g., t-PA; see U.S. Patent No. 5,641,655) or synthesized *de novo*. The secretory signal sequence is operably linked to the DNA sequence encoding the protein of interest, i.e., the two sequences are joined in the correct reading frame and positioned to direct the newly synthesized protein into the secretory pathway of the host cell. Secretory signal sequences are commonly positioned 5' to the DNA sequence encoding the protein of interest, although certain secretory signal sequences may be positioned elsewhere in the DNA sequence of interest (see, e.g., Welch et al., U.S. Patent No. 5,037,743; Holland et al., U.S. Patent No. 5,143,830).

Cultured mammalian cells are suitable hosts for use within the present Methods for introducing exogenous DNA into mammalian host cells include calcium phosphate-mediated transfection (Wigler et al., Cell 14:725, 1978; Corsaro and Pearson, Somatic Cell Genetics 7:603, 1981: Graham and Van der Eb, Virology 52:456, 1973), electroporation (Neumann et al., EMBO J. 1:841-845, 1982), DEAE-dextran mediated transfection (Ausubel et al., ibid.), and liposome-mediated transfection (Hawley-Nelson et al., Focus 15:73, 1993; Ciccarone et al., Focus 15:80, 1993). The production of recombinant polypeptides in cultured mammalian cells is disclosed by, for example, Levinson et al., U.S. Patent No. 4,713,339; Hagen et al., U.S. Patent No. 4,784,950; Palmiter et al., U.S. Patent No. 4,579,821; and Ringold, U.S. Patent No. 4,656,134. Suitable cultured mammalian cells include the COS-1 (ATCC No. CRL 1650), COS-7 (ATCC No. CRL 1651), BHK (ATCC No. CRL 1632), BHK 570 (ATCC No. CRL 10314), 293 (ATCC No. CRL 1573; Graham et al., J. Gen. Virol. 36:59-72, 1977) and Chinese hamster ovary (e.g. CHO-K1; ATCC No. CCL 61) cell lines. Additional suitable cell lines are known in the art and available from public depositories such as the American Type Culture Collection, Rockville, Maryland. In general, strong transcription promoters are preferred, such as promoters from SV-40 or cytomegalovirus. See, e.g., U.S. Patent No. 4,956,288. Other suitable promoters include those from metallothionein genes (U.S. Patent Nos. 4,579,821 and 4,601,978) and the adenovirus major late promoter. Within an alternative embodiment, adenovirus vectors can be employed. See, for example, Garnier et al., Cytotechnol. 15:145-55, 1994.

Drug selection is generally used to select for cultured mammalian cells into which foreign DNA has been inserted. Such cells are commonly referred to as "transfectants". Cells that have been cultured in the presence of the selective agent and

are able to pass the gene of interest to their progeny are referred to as "stable transfectants." An exemplary selectable marker is a gene encoding resistance to the antibiotic neomycin. Selection is carried out in the presence of a neomycin-type drug, such as G-418 or the like. Selection systems can also be used to increase the expression level of the gene of interest, a process referred to as "amplification." Amplification is carried out by culturing transfectants in the presence of a low level of the selective agent and then increasing the amount of selective agent to select for cells that produce high levels of the products of the introduced genes. An exemplary amplifiable selectable marker is dihydrofolate reductase, which confers resistance to methotrexate. Other drug resistance genes (e.g. hygromycin resistance, multi-drug resistance, puromycin acetyltransferase) can also be used.

Insect cells can be infected with recombinant baculovirus, commonly derived from *Autographa californica* nuclear polyhedrosis virus (AcNPV). See, King and Possee, The Baculovirus Expression System: A Laboratory Guide, London, Chapman & Hall; O'Reilly et al., Baculovirus Expression Vectors: A Laboratory Manual, New York, Oxford University Press., 1994; and Richardson, Ed., Baculovirus Expression Protocols. Methods in Molecular Biology, Humana Press, Totowa, NJ, 1995. Recombinant baculovirus can also be produced through the use of a transposon-based system described by Luckow et al. (*J. Virol.* 67:4566-4579, 1993). This system, which utilizes transfer vectors, is commercially available in kit form (Bac-to-Bac™ kit; Life Technologies, Rockville, MD). See also, Hill-Perkins and Possee, *J. Gen. Virol.* 71:971-976, 1990; Bonning et al., *J. Gen. Virol.* 75:1551-1556, 1994; and Chazenbalk and Rapoport, *J. Biol. Chem.* 270:1543-1549, 1995.

For protein production, the recombinant virus is used to infect host cells, typically a cell line derived from the fall armyworm, *Spodoptera frugiperda* (e.g., Sf9 or Sf21 cells) or *Trichoplusia ni* (e.g., High FiveTM cells; Invitrogen, Carlsbad, CA). See, in general, Glick and Pasternak, <u>Molecular Biotechnology: Principles and Applications of Recombinant DNA</u>, ASM Press, Washington, D.C., 1994. See also, U.S. Patent No. 5,300,435. Serum-free media are used to grow and maintain the cells. Suitable media formulations are known in the art and can be obtained from commercial suppliers. The cells are grown up from an inoculation density of approximately 2-5 x 10⁵ cells to a density of 1-2 x 10⁶ cells, at which time a recombinant viral stock is added at a multiplicity of infection (MOI) of 0.1 to 10, more typically near 3. Procedures used are generally described in available laboratory manuals (e.g., King and Possee, *ibid.*; O'Reilly et al., *ibid.*; Richardson, *ibid.*). See also, Guarino et al., U.S. Patent No. 5,162,222 and WIPO publication WO 94/06463.

Fungal cells, including yeast cells, can also be used within the present invention. Yeast species of particular interest in this regard include Saccharomyces cerevisiae, Pichia pastoris, and Pichia methanolica. Methods for transforming S. cerevisiae cells with exogenous DNA and producing recombinant polypeptides therefrom are disclosed by, for example, Kawasaki, U.S. Patent No. 4,599,311; Kawasaki et al., U.S. Patent No. 4,931,373; Brake, U.S. Patent No. 4,870,008; Welch et al., U.S. Patent No. 5,037,743; and Murray et al., U.S. Patent No. 4,845,075. Transformed cells are selected by phenotype determined by the selectable marker, commonly drug resistance or the ability to grow in the absence of a particular nutrient (e.g., leucine). A preferred vector system for use in Saccharomyces cerevisiae is the POT1 vector system disclosed by Kawasaki et al. (U.S. Patent No. 4,931,373), which allows transformed cells to be selected by growth in glucose-containing media. Suitable promoters and terminators for use in yeast include those from glycolytic enzyme genes (see, e.g., Kawasaki, U.S. Patent No. 4,599,311; Kingsman et al., U.S. Patent No. 4,615,974; and Bitter, U.S. Patent No. 4,977,092) and alcohol dehydrogenase genes. See also U.S. Patents Nos. 4,990,446; 5,063,154; 5,139,936 and 4,661,454.

Transformation systems for other yeasts, including Hansenula polymorpha, Schizosaccharomyces pombe, Kluyveromyces lactis, Kluyveromyces 20 fragilis, Ustilago maydis, Pichia pastoris, Pichia methanolica, Pichia guillermondii and Candida maltosa are known in the art. See, for example, Gleeson et al., J. Gen. Microbiol. 132:3459-3465, 1986 and Cregg, U.S. Patent No. 4,882,279. Aspergillus cells may be utilized according to the methods of McKnight et al., U.S. Patent No. 4,935,349. Methods for transforming Acremonium chrysogenum are disclosed by Sumino et al., U.S. Patent No. 5,162,228. Methods for transforming Neurospora are disclosed by Lambowitz, U.S. Patent No. 4,486,533. Production of recombinant proteins in Pichia methanolica is disclosed in U.S. Patents No. 5,716,808, 5,736,383, 5,854,039, and 5,888,768; and WIPO publications WO 99/14347 and WO 99/14320.

Other higher cukaryotic cells, including plant cells and avian cells, can also be used as hosts according to methods commonly known in the art. For example, the use of *Agrobacterium rhizogenes* as a vector for expressing genes in plant cells has been reviewed by Sinkar et al., *J. Biosci.* (*Bangalore*) 11:47-58, 1987.

Prokaryotic host cells, including strains of the bacteria *Escherichia coli*, *Bacillus* and other genera are also useful host cells within the present invention. Techniques for transforming these hosts and expressing foreign DNA sequences cloned therein are well known in the art (see, e.g., Sambrook et al., ibid.). When expressing a polypeptide in bacteria such as *E. coli*, the polypeptide may be retained in the

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cytoplasm, typically as insoluble granules, or may be directed to the periplasmic space by a bacterial secretion sequence. In the former case, the cells are lysed, and the granules are recovered and denatured using, for example, guanidine isothiocyanate or urea. The denatured polypeptide can then be refolded and dimerized by diluting the denaturant, such as by dialysis against a solution of urea and a combination of reduced and oxidized glutathione, followed by dialysis against a buffered saline solution. In the latter case, the polypeptide can be recovered from the periplasmic space in a soluble and functional form by disrupting the cells (by, for example, sonication or osmotic shock) to release the contents of the periplasmic space and recovering the protein. thereby obviating the need for denaturation and refolding.

Transformed or transfected host cells are cultured according to conventional procedures in a culture medium containing nutrients and other components required for the growth of the chosen host cells. A variety of suitable media, including defined media and complex media, are known in the art and generally 15 include a carbon source, a nitrogen source, essential amino acids, vitamins and minerals. Media may also contain such components as growth factors or serum, as required. The growth medium will generally select for cells containing the exogenously added DNA by, for example, drug selection or deficiency in an essential nutrient which is complemented by the selectable marker carried on the expression vector or co-transfected into the host cell.

It is preferred to purify the polypeptides and proteins of the present invention to ≥80% purity, more preferably to ≥90% purity, even more preferably ≥95% purity, and particularly preferred is a pharmaceutically pure state, that is greater than 99.9% pure with respect to contaminating macromolecules, particularly other proteins and nucleic acids, and free of infectious and pyrogenic agents. Preferably, a purified polypeptide or protein is substantially free of other polypeptides or proteins. particularly those of animal origin.

Expressed recombinant proteins (including single polypeptide chains, chimeric polypeptides, and polypeptide multimers) are purified by conventional protein purification methods, typically by a combination of chromatographic techniques. See, in general, Affinity Chromatography: Principles & Methods, Pharmacia LKB Biotechnology, Uppsala, Sweden, 1988; and Scopes, Protein Purification: Principles and Practice, Springer-Verlag, New York, 1994. Proteins comprising a polyhistidine affinity tag (typically about 6 histidine residues) are purified by affinity chromatography on a nickel chelate resin. See, for example, Houchuli et al., Bio/Technol. 6: 1321-1325, 1988. Proteins comprising a glu-glu tag can be purified by immunoaffinity chromatography essentially as disclosed by Grussenmeyer et al., ibid.

Proteins comprising other affinity tags can be purified by appropriate affinity chromatography methods, which are known in the art.

Proteins of the present invention and fragments thereof can also be prepared through chemical synthesis according to methods known in the art, including exclusive solid phase synthesis, partial solid phase methods, fragment condensation or classical solution synthesis. See, for example, Merrifield, *J. Am. Chem. Soc.* 85:2149, 1963; Stewart et al., Solid Phase Peptide Synthesis (2nd edition), Pierce Chemical Co., Rockford, IL, 1984; Bayer and Rapp, *Chem. Pept. Prot.* 3:3, 1986; and Atherton et al., Solid Phase Peptide Synthesis: A Practical Approach, IRL Press, Oxford, 1989.

Using methods known in the art, the proteins of the present invention can be prepared in a variety of modified or derivatized forms. For example, the proteins can be prepared glycosylated or non-glycosylated; pegylated or non-pegylated; and may or may not include an initial methionine amino acid residue.

Biological activities of the proteins of the present invention can be measured in vitro using cultured cells or in vivo by administering molecules of the claimed invention to the appropriate animal model. Many such assays and models are known in the art. Guidance in initial assay selection is provided by structural predictions and sequence alignments. However, even if no functional prediction is made, the activity of a protein can be elucidated by known methods, including, for example, screening a variety of target cells for a biological response, other in vitro assays, expression in a host animal, or through the use of transgenic and/or "knockout" animals. Through the application of robotics, many in vitro assays can be adapted to rapid, high-throughput screeing of a large number of samples. Target cells for use in activity assays include, without limitation, vascular cells (especially endothelial cells and smooth muscle cells), hematopoietic (myeloid and lymphoid) cells, liver cells (including hepatocytes, fenestrated endothelial cells, Kupffer cells, and Ito cells), fibroblasts (including human dermal fibroblasts and lung fibroblasts), neurite cells (including astrocytes, glial cells, dendritic cells, and PC-12 cells), fetal lung cells, articular synoviocytes, pericytes, chondrocytes, osteoblasts, adipocytes, and prostate epithelial cells. Endothelial cells and hematopoietic cells are derived from a common ancestral cell, the hemangioblast (Choi et al., Development 125:725-732, 1998).

Biological activity can be measured with a silicon-based biosensor microphysiometer that measures the extracellular acidification rate or proton excretion associated with receptor binding and subsequent physiologic cellular responses. An exemplary such device is the CytosensorTM Microphysiometer manufactured by Molecular Devices, Sunnyvale, CA. A variety of cellular responses, such as cell proliferation, ion transport, energy production, inflammatory response, regulatory and

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receptor activation, and the like, can be measured by this method. See, for example, McConnell et al., Science 257:1906-1912, 1992; Pitchford et al., Meth. Enzymol. 228:84-108, 1997; Arimilli et al., J. Immunol. Meth. 212:49-59, 1998; and Van Liefde et al., Eur. J. Pharmacol. 346:87-95, 1998. The microphysiometer can be used for assaying adherent or non-adherent eukaryotic or prokaryotic cells. By measuring extracellular acidification changes in cell media over time, the microphysiometer directly measures cellular responses to various stimuli, including agonistic and antagonistic stimuli. Preferably, the microphysiometer is used to measure responses of a eukaryotic cell known to be responsive to the protein of interest, compared to a control eukaryotic cell that does not respond to the protein of interest. Responsive eukaryotic cells comprise cells into which a receptor for the protein of interest has been transfected, as well as naturally responsive cells. Differences in the response of cells exposed to the protein of interest, relative to a control not so exposed, are a direct measurement of protein-modulated cellular responses. Such responses can be assayed under a variety of stimuli. The present invention thus provides methods of identifying agonists and antagonists of proteins of interest, comprising providing cells responsive to a selected protein, culturing a first portion of the cells in the absence of a test compound, culturing a second portion of the cells in the presence of a test compound, and detecting a change in a cellular response of the second portion of the cells as compared to the first portion of the cells. The change in cellular response is shown as a measurable change in extracellular acidification rate. Culturing a third portion of the cells in the presence of the protein of interest and the absence of a test compound provides a positive control and a control to compare the agonist activity of a test compound with that of the protein of interest. Antagonists can be identified by exposing the cells to the protein of interest in the presence and absence of the test compound, whereby a reduction in protein-stimulated activity is indicative of antagonist activity in the test compound.

Assays measuring cell proliferation or differentiation are well known in the art. For example, assays measuring proliferation include such assays as chemosensitivity to neutral red dye (Cavanaugh et al., *Investigational New Drugs* 8:347-354, 1990), incorporation of radiolabelled nucleotides (as disclosed by, e.g., Raines and Ross, *Methods Enzymol.* 109:749-773, 1985; Wahl et al., *Mol. Cell Biol.* 8:5016-5025, 1988; and Cook et al., *Analytical Biochem.* 179:1-7, 1989), incorporation of 5-bromo-2'-deoxyuridine (BrdU) in the DNA of proliferating cells (Porstmann et al., *J. Immunol. Methods* 82:169-179, 1985), and use of tetrazolium salts (Mosmann, *J. Immunol. Methods* 65:55-63, 1983; Alley et al., *Cancer Res.* 48:589-601, 1988; Marshall et al., *Growth Reg.* 5:69-84, 1995; and Scudiero et al., *Cancer Res.* 48:4827-

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4833, 1988). Differentiation can be assayed using suitable precursor cells that can be induced to differentiate into a more mature phenotype. Assays measuring differentiation include, for example, measuring cell-surface markers associated with stage-specific expression of a tissue, enzymatic activity, functional activity or morphological changes (Watt, FASEB, 5:281-284, 1991; Francis, Differentiation 57:63-75, 1994; Raes, Adv. Anim. Cell Biol. Technol. Bioprocesses, 161-171, 1989). Effects of a protein on tumor cell growth and metastasis can be analyzed using the Lewis lung carcinoma model, for example as described by Cao et al., J. Exp. Med. 182:2069-2077, 1995. Activity of a protein on cells of neural origin can be analyzed using assays that measure effects on neurite growth as disclosed below.

In vitro assays for pro- and anti-inflammatory activity are known in the art. Exemplary activity assays include mitogenesis assays in which IL-1 responsive cells (e.g., D10.N4.M cells) are incubated in the presence of IL-1 or a test protein for 72 hours at 37°C in a 5% CO₂ atmosphere. IL-2 (and optionally IL-4) is added to the culture medium to enhance sensitivity and specificity of the assay. ³H-thymidine is then added, and incubation is continued for six hours. The amount of label incorporated is indicative of agonist activity. See, Hopkins and Humphreys, J. Immunol. Methods 120:271-276, 1989; Greenfeder et al., J. Biol. Chem. 270:22460-22466, 1995. Stimulation of cell proliferation can also be measured using thymocytes cultured in a test protein in combination with phytohemagglutinin. IL-1 is used as a control. Proliferation is detected as ³H-thymidine incorporation or metabolic breakdown of (MTT) (Mosman, ibid.).

Protein activity may also be detected using assays designed to measure induction of one or more growth factors or other macromolecules. Preferred such assays include those for determining the presence of hepatocyte growth factor (HGF), epidermal growth factor (EGF), transforming growth factor alpha (TGF α), interleukin-6 (IL-6), VEGF, acidic fibroblast growth factor (aFGF), angiogenin, and other macromolecules produced by the liver. Suitable assays include mitogenesis assays using target cells responsive to the macromolecule of interest, receptor-binding assays, competition binding assays, immunological assays (e.g., ELISA), and other formats known in the art. Metalloprotease secretion is measured from treated primary human dermal fibroblasts, synoviocytes and chondrocytes. The relative levels of collagenase, gelatinase and stromalysin produced in response to culturing a target cell in the presence of a protein of interest is measured using zymogram gels (Loita and Stetler-Stevenson, *Cancer Biology* 1:96-106, 1990). Procollagen/collagen synthesis by dermal fibroblasts and chondrocytes in response to a test protein is measured using ³H-proline incorporation into nascent secreted collagen.

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SDS-PAGE followed by autoradiography (Unemori and Amento, *J. Biol. Chem.* 265: 10681-10685, 1990). Glycosaminoglycan (GAG) secretion from dermal fibroblasts and chondrocytes is measured using a 1,9-dimethylmethylene blue dye binding assay (Farndale et al., *Biochim. Biophys. Acta* 883:173-177, 1986). Collagen and GAG assays are also carried out in the presence of IL-1β or TGF-β to examine the ability of a protein to modify the established responses to these cytokines.

Monocyte activation assays are carried out (1) to look for the ability of a protein of interest to further stimulate monocyte activation, and (2) to examine the ability of a protein of interest to modulate attachment-induced or endotoxin-induced monocyte activation (Fuhlbrigge et al., *J. Immunol.* 138: 3799-3802, 1987). IL-1 β and TNF α levels produced in response to activation are measured by ELISA (Biosource, Inc. Camarillo, CA). Monocyte/macrophage cells, by virtue of CD14 (LPS receptor), are exquisitely sensitive to endotoxin, and proteins with moderate levels of endotoxin-like activity will activate these cells.

Other metabolic effects of proteins can be measured by culturing target cells in the presence and absence of a protein and observing changes in adipogenesis, gluconeogenesis, glycogenolysis, lipogenesis, glucose uptake, or the like. Suitable assays are known in the art.

Hematopoietic activity of proteins can be assayed on various hematopoietic cells in culture. Preferred assays include primary bone marrow colony assays and later stage lineage-restricted colony assays, which are known in the art (e.g., Holly et al., WIPO Publication WO 95/21920). Marrow cells plated on a suitable semi-solid medium (e.g., 50% methylcellulose containing 15% fetal bovine serum, 10% bovine serum albumin, and 0.6% PSN antibiotic mix) are incubated in the presence of test polypeptide, then examined microscopically for colony formation. Known hematopoietic factors are used as controls. Mitogenic activity of a protein of interest on hematopoietic cell lines can be measured as disclosed above.

Cell migration is assayed essentially as disclosed by Kähler et al. (Arteriosclerosis, Thrombosis, and Vascular Biology 17:932-939, 1997). A protein is considered to be chemotactic if it induces migration of cells from an area of low protein concentration to an area of high protein concentration. A typical assay is performed using modified Boyden chambers with a polystryrene membrane separating the two chambers (Transwell; Corning Costar Corp.). The test sample, diluted in medium containing 1% BSA, is added to the lower chamber of a 24-well plate containing Transwells. Cells are then placed on the Transwell insert that has been pretreated with 0.2% gelatin. Cell migration is measured after 4 hours of incubation at 37°C. Non-migrating cells are wiped off the top of the Transwell membrane, and cells

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attached to the lower face of the membrane are fixed and stained with 0.1% crystal violet. Stained cells are then extracted with 10% acetic acid and absorbance is measured at 600 nm. Migration is then calculated from a standard calibration curve. Cell migration can also be measured using the matrigel method of Grant et al. ("Angiogenesis as a component of epithelial-mesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997).

Proteins can be assayed for the ability to modulate axon guidance and growth. Suitable assays that detect changes in neuron growth patterns include, for example, those disclosed in Hastings, WIPO Publication WO 97/29189 and Walter et al., Development 101:685-96, 1987. Assays to measure the effects on neuron growth are well known in the art. For example, the C assay (e.g., Raper and Kapfhammer, Neuron 4:21-9, 1990 and Luo et al., Cell 75:217-27, 1993) can be used to determine collapsing activity of a protein of interest on growing neurons. Other methods that can assess protein-induced inhibition of neurite extension or divert such extension are also known. See, Goodman, Annu. Rev. Neurosci. 19:341-77, 1996. Conditioned media from cells expressing a protein of interest, or aggregates of such cells, can by placed in a gel matrix near suitable neural cells, such as dorsal root ganglia (DRG) or sympathetic ganglia explants, which have been co-cultured with nerve growth factor. Compared to control cells, protein-induced changes in neuron growth can be measured (as disclosed by, for example, Messersmith et al., Neuron 14:949-59, 1995 and Puschel et al., Neuron 14:941-8, 1995). Neurite outgrowth can be measured using neuronal cell suspensions grown in the presence of molecules of the present invention. See, for example, O'Shea et al., Neuron 7:231-7, 1991 and DeFreitas et al., Neuron 15:333-43, 1995.

Cell adhesion activity is assayed essentially as disclosed by LaFleur et al. (*J. Biol. Chem.* 272:32798-32803, 1997). Briefly, microtiter plates are coated with the test protein, non-specific sites are blocked with BSA, and cells (such as smooth muscle cells, leukocytes, or endothelial cells) are plated at a density of approximately $10^4 - 10^5$ cells/well. The wells are incubated at 37°C (typically for about 60 minutes), then non-adherent cells are removed by gentle washing. Adhered cells are quantitated by conventional methods (e.g., by staining with crystal violet, lysing the cells, and determining the optical density of the lysate). Control wells are coated with a known adhesive protein, such as fibronectin or vitronectin.

Assays for angiogenic activity are also known in the art. For example, the effect of a protein of interest on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science

246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Other suitable assays include microinjection of early stage quail (Coturnix coturnix japonica) embryos as disclosed by Drake et al. (Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995); the rodent model of corneal neovascularization disclosed by Muthukkaruppan and Auerbach (Science 205:1416-1418, 1979), wherein a test substance is inserted into a pocket in the cornea of an inbred mouse; and the hampster cheek pouch assay (Höckel et al., Arch. Surg. 128:423-429, 1993). Induction of vascular permeability, which is indicative of angiogenic activity, is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, J. Physiol. 118:228-257, 1952; Feng et al., J. Exp. Med. <u>183</u>:1981-1986, 1996). In vitro assays for angiogenic activity include the tridimensional collagen gel matrix model (Pepper et al. Biochem. Biophys. Res. Comm. 189:824-831, 1992 and Ferrara et al., Ann. NY Acad. Sci. 732:246-256, 1995), which measures the formation of tube-like structures by microvascular endothelial cells; and matrigel models (Grant et al., "Angiogenesis as a component of epithelialmesenchymal interactions" in Goldberg and Rosen, Epithelial-Mesenchymal Interaction in Cancer, Birkhäuser Verlag, 1995, 235-248; Baatout, Anticancer Research 17:451-456, 1997), which are used to determine effects on cell migration and tube formation by endothelial cells seeded in matrigel, a basement membrane extract enriched in laminin. It is preferred to carry out angiogenesis assays in the presence and absence of vascular endothelial growth factor (VEGF) to assess possible combinatorial effects. It is also preferred to use VEGF as a control within in vivo assays.

Receptor binding can be measured by the competition binding method of Labriola-Tompkins et al., *Proc. Natl. Acad. Sci. USA* 88:11182-11186, 1991. In an exemplary assay for IL-1 receptor binding, membranes pepared from EL-4 thymoma cells (Paganelli et al., *J. Immunol.* 138:2249-2253, 1987) are incubated in the presence of the test protein for 30 minutes at 37°C. Labeled IL-1 α or IL-1 β is then added and the incubation is continued for 60 minutes. The assay is terminated by membrane filtration. The amount of bound label is determined by conventional means (e.g., γ counter). In an alternative assay, the ability of a test protein to compete with labeled IL-1 for binding to cultured human dermal fibroblasts is measured according to the method of Dower et al. (*Nature* 324:266-268, 1986). Briefly, cells are incubated in a round-bottomed, 96-well plate in a suitable culture medium (e.g., RPMI 1640 containing 1% BSA, 0.1% Na azide, and 20 mM HEPES pH 7.4) at 8°C on a rocker

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platform in the presence of labeled IL-1. Various concentrations of test protein are added. After the incubation (typically about two hours), cells are separated from unbound label by centrifuging 60-µl aliquots through 200 µl of phthalate oils in 400-µl polyethylene centrifuge tubes and excising the tips of the tubes with a razor blade as disclosed by Segal and Hurwitz, *J. Immunol.* 118:1338-1347, 1977. Receptor binding assays for other cell types are known in the art. See, for example, Bowen-Pope and Ross, *Methods Enzymol.* 109:69-100, 1985.

Receptor binding can also be measured using immobilized receptors or ligand-binding receptor fragments. For example, an immobilized receptor can be exposed to its labeled ligand and unlabeled test protein, whereby a reduction in labeled ligand binding compared to a control is indicative of receptor-binding activity in the test protein. Within another format, a receptor or ligand-binding receptor fragment is immobilized on a biosensor (e.g., BIACoreTM, Pharmacia Biosensor, Piscataway, NJ) and binding is determined. Antagonists of the native ligand will exhibit receptor binding but will exhibit essentially no activity in appropriate activity assays or will reduce the ligand-mediated response when combined with the native ligand. In view of the low level of receptor occupancy required to produce a response to some ligands (e.g., IL-1), a large excess of antagonist (typically a 10- to 1000-fold molar excess) may be necessary to neutralize ligand activity.

Receptor activation can be detected in target cells by: (1) measurement of adenylate cyclase activity (Salomon et al., Anal. Biochem. 58:541-48, 1974; Alvarez and Daniels, Anal. Biochem. 187:98-103, 1990); (2) measurement of change in intracellular cAMP levels using conventional radioimmunoassay methods (Steiner et al., J. Biol. Chem. 247:1106-13, 1972; Harper and Brooker, J. Cyc. Nucl. Res. 1:207-18, 1975); or (3) through use of a cAMP scintillation proximity assay (SPA) method (such as available from Amersham Corp., Arlington Heights, IL).

Proteins can be tested for serine protease activity or proteinase inhibitory activity using conventional assays. Substrate cleavage is conveniently assayed using a tetrapeptide that mimics the cleavage site of the natural substrate and which is linked, via a peptide bond, to a carboxyl-terminal para-nitro-anilide (pNA) group. The protease hydrolyzes the bond between the fourth amino acid residue and the pNA group, causing the pNA group to undergo a dramatic increase in absorbance at 405 nm. Suitable substrates can be synthesized according to known methods or obtained from commercial suppliers. Inhibitory activity is measured by adding a test sample to a reaction mixture containing enzyme and substrate, and comparing the observed enzyme activity to a control (without the test sample). A variety of such assays are known in the art, including assays measuring inhibition of trypsin,

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chymotrypsin, plasmin, cathepsin G, and human leukocyte elastase. See, for example, Petersen et al., Eur. J. Biochem. 235:310-316, 1996. In a typical procedure, the inhibitory activity of a test compound is measured by incubating the test compound with the proteinase, then adding an appropriate substrate, typically a chromogenic peptide substrate. See, for example, Norris et al. (Biol. Chem. Hoppe-Seyler 371:37-42, 1990). Various concentrations of the inhibitor are incubated in the presence of trypsin, plasmin, and plasma kallikrein in a low-salt buffer at pH 7.4, 25°C. After 30 minutes, the residual enzymatic activity is measured by the addition of a chromogenic substrate (e.g., S2251 (D-Val-Leu-Lys-Nan) or S2302 (D-Pro-Phe-Arg-Nan), available from Kabi, Stockholm, Sweden) and a 30-minute incubation. Inhibition of enzyme activity is indicated by a decrease in absorbance at 405 nm or fluorescence Em at 460 nm. From the results, the apparent inhibition constant K_i is calculated. When a serine protease is prepared as an active precursor (e.g., comprising N-terminal residues 1-109 of SEQ ID NO:2), it is activated by cleavage with a suitable protease (e.g., furin (Steiner et al., J. Biol. Chem. 267:23435-23438, 1992)) prior to assay. Assays of this type are well known in the art. See, for example, Lottenberg et al., Thrombosis Research 28:313-332, 1982; Cho et al., Biochem. 23:644-650, 1984; Foster et al., Biochem. 26:7003-7011, 1987). The inhibition of coagulation factors (e.g., factor VIIa, factor Xa) can be measured using chromogenic substrates or in conventional coagulation assays (e.g., clotting time of normal human plasma; Dennis et al., J. Biol. Chem. 270:25411-25417, 1995).

Blood coagulation and chromogenic assays, which can be used to detect both procoagulant, anticoagulant, and thrombolytic activities, are known in the art. For example, pro- and anticoagulant activities can be measured in a one-stage clotting assay using platelet-poor or factor-deficient plasma (Levy and Edgington, *J. Exp. Med.* 151:1232-1243, 1980; Schwartz et al., *J. Clin. Invest.* 67:1650-1658, 1981). As disclosed by Anderson et al. (*Proc. Natl. Acad. Sci. USA* 96:11189-11193, 1999), the effect of a test compound on platelet activation can be determined by a change in turbidity, and the procoagulant activity of activated platelets can be determined in a phospholipid-dependent coagulation assay. Activation of thrombin can be determined by hydrolysis of peptide p-nitroanilide substrates as disclosed by Lottenberg et al. (*Thrombosis Res.* 28:313-332, 1982). Other procoagulant, anticoagulant, and thrombolytic activities can be measured using appropriate chromogenic substrates, a variety of which are available from commercial suppliers. See, for example, Kettner and Shaw, *Methods Enzymol.* 80:826-842, 1981.

Anti-microbial activity of proteins is evaluated by techniques that are known in the art. For example, anti-microbial activity can be assayed by evaluating the

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sensitivity of microbial cell cultures to test agents and by evaluating the protective effect of test agents on infected mice. See, for example, Musiek et al., Antimicrob. Agents Chemothr. 3:40, 1973. Antiviral activity can also be assessed by protection of mammalian cell cultures. Known techniques for evaluating anti-microbial activity include, for example, Barsum et al., Eur. Respir. J. 8:709-714, 1995; Sandovsky-Losica et al., J. Med. Vet. Mycol (England) 28:279-287, 1990; Mehentee et al., J. Gen. Microbiol (England) 135(:2181-2188, 1989; and Segal and Savage, J. Med. Vet. Mycol. 24:477-479, 1986. Assays specific for anti-viral activity include, for example, those described by Daher et al., J. Virol. 60:1068-1074, 1986.

The assays disclosed above can be modified by those skilled in the art to detect the presence of agonists and antagonists of a selected protein of interest.

Expression of a polynucleotide encoding a protein of interest in animals provides models for further study of the biological effects of overproduction or inhibition of protein activity *in vivo*. Polynucleotides and antisense polynucleotides can be introduced into test animals, such as mice, using viral vectors or naked DNA, or transgenic animals can be produced.

One *in vivo* approach for assaying proteins of the present invention utilizes viral delivery systems. Exemplary viruses for this purpose include adenovirus, herpesvirus, retroviruses, vaccinia virus, and adeno-associated virus (AAV). Adenovirus, a double-stranded DNA virus, is currently the best studied gene transfer vector for delivery of heterologous nucleic acids. For review, see Becker et al., *Meth. Cell Biol.* 43:161-89, 1994; and Douglas and Curiel, *Science & Medicine* 4:44-53, 1997. The adenovirus system offers several advantages. Adenovirus can (i) accommodate relatively large DNA inserts; (ii) be grown to high-titer; (iii) infect a broad range of mammalian cell types; and (iv) be used with many different promoters including ubiquitous, tissue specific, and regulatable promoters. Because adenoviruses are stable in the bloodstream, they can be administered by intravenous injection.

By deleting portions of the adenovirus genome, larger inserts (up to 7 kb) of heterologous DNA can be accommodated. These inserts can be incorporated into the viral DNA by direct ligation or by homologous recombination with a cotransfected plasmid. In an exemplary system, the essential E1 gene is deleted from the viral vector, and the virus will not replicate unless the E1 gene is provided by the host cell (e.g., the human 293 cell line). When intravenously administered to intact animals, adenovirus primarily targets the liver. If the adenoviral delivery system has an E1 gene deletion, the virus cannot replicate in the host cells. However, the host's tissue (e.g., liver) will express and process (and, if a signal sequence is present, secrete) the

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heterologous protein. Secreted proteins will enter the circulation in the highly vascularized liver, and effects on the infected animal can be determined.

An alternative method of gene delivery comprises removing cells from the body and introducing a vector into the cells as a naked DNA plasmid. The transformed cells are then re-implanted in the body. Naked DNA vectors are introduced into host cells by methods known in the art, including transfection, electroporation, microinjection, transduction, cell fusion, DEAE dextran, calcium phosphate precipitation, use of a gene gun, or use of a DNA vector transporter. See, Wu et al., *J. Biol. Chem.* 263:14621-14624, 1988; Wu et al., *J. Biol. Chem.* 267:963-967, 1992; and Johnston and Tang, *Meth. Cell Biol.* 43:353-365, 1994.

Transgenic mice, engineered to express a gene encoding a protein of interest, and mice that exhibit a complete absence of gene function, referred to as "knockout mice" (Snouwaert et al., Science 257:1083, 1992), can also be generated (Lowell et al., Nature 366:740-742, 1993). These mice can be employed to study the gene of interest and the protein encoded thereby in an in vivo system. Transgenic mice are particularly useful for investigating the role of proteins in early development in that they allow the identification of developmental abnormalities or blocks resulting from the over- or underexpression of a specific factor. See also, Maisonpierre et al., Science 277:55-60, 1997 and Hanahan, Science 277:48-50, 1997. Preferred promoters for transgenic expression include promoters from metallothionein and albumin genes. As disclosed above, the human sequences provided herein can be used to clone orthologous polynucleotides, which may be preferred for use in generating transgenic and knockout animals.

Antisense methodology can be used to inhibit gene transcription to examine the effects of such inhibition *in vivo*. Polynucleotides that are complementary to a segment of a protein-encoding polynucleotide are designed to bind to the encoding mRNA and to inhibit translation of such mRNA. Such antisense oligonucleotides can also be used to inhibit expression of protein-encoding genes in cell culture.

Biological activities of test proteins can also be measured in animal models by administering the test protein, by itself or in combination with other agents, including other proteins. Using such models facilitates the assay of the test protein by itself or as an inhibitor or modulator of another agent, and also facilitates the measurement of combinatorial effects of bioactive compounds.

Anti-inflammatory activity can be tested in animal models of inflammatory disease. For example, animal models of psoriasis include the analysis of histological alterations in adult mouse tail epidermis (Hofbauer et al, *Brit. J. Dermatol.*)

118:85-89, 1988; Bladon et al., Arch Dermatol. Res. 277:121-125, 1985). In this model, anti-psoriatic activity is indicated by the induction of a granular layer and orthokeratosis in areas of scale between the hinges of the tail epidermis. Typically, a topical ointment comprising a test compound is applied daily for seven consecutive days, then the animal is sacrificed, and tail skin is examined histologically. An additional model is provided by grafting psoriatic human skin to congenitally athymic (nude) mice (Krueger et al., J. Invest. Dermatol. 64:307-312, 1975). Such grafts have been shown to retain the characteristic histology for up to eleven weeks. As in the mouse tail model, the test composition is applied to the skin at predetermined intervals for a period of one to several weeks, at which time the animals are sacrificed and the skin grafts examined histologically. A third model has been disclosed by Fretland et al. (Inflammation 14:727-739, 1990). Briefly, inflammation is induced in guinea pig epidermis by topically applying phorbol ester (phorbol-12-myristate-13-acetate; PMA), typically at ca. 2 g/ml in acetone, to one ear and vehicle to the contralateral ear. Test compounds are applied concurrently with the PMA, or may be given orally. Histological analysis is performed at 96 hours after application of PMA. This model duplicates many symptoms of human psoriasis, including edema, inflammatory cell diapedesis and infiltration, high LTB4 levels and epidermal proliferation.

Cerebral ischemia can be studied in a rat model as disclosed by Relton et al. (*ibid.*) and Loddick et al. (*ibid.*).

The effect of a test protein on primordial endothelial cells in angiogenesis can be assayed in the chick chorioallantoic membrane angiogenesis assay (Leung, Science 246:1306-1309, 1989; Ferrara, Ann. NY Acad. Sci. 752:246-256, 1995). Briefly, a small window is cut into the shell of an eight-day old fertilized egg, and a test substance is applied to the chorioallantoic membrane. After 72 hours, the membrane is examined for neovascularization. Embryo microinjection of early stage quail (Coturnix coturnix japonica) embryos can also be used (Drake et al., Proc. Natl. Acad. Sci. USA 92:7657-7661, 1995). Briefly, a solution containing the protein is injected into the interstitial space between the endoderm and the splanchnic mesoderm of early-stage embryos using a micropipette and micromanipulator system. After injection, embryos are placed ventral side down on a nutrient agar medium and incubated for 7 hours at 37°C in a humidified CO₂/air mixture (10%/90%). Vascular development is assessed by microscopy of fixed, whole-mounted embryos and sections.

Stimulation of coronary collateral growth can be measured in known animal models, including a rabbit model of peripheral limb ischemia and hind limb ischemia and a pig model of chronic myocardial ischemia (Ferrara et al., *Endocrine*

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Reviews 18:4-25, 1997). Test proteins are assayed in the presence and absence of VEGF and basic FGF to test for combinatorial effects. These models can be modified by the use of adenovirus or naked DNA for gene delivery as disclosed in more detail above, resulting in local expression of the test protein(s).

Angiogenic activity can also be tested in a rodent model of corneal neovascularization as disclosed by Muthukkaruppan and Auerbach, *Science* 205:1416-1418, 1979, wherein a test substance is inserted into a pocket in the cornea of an inbred mouse. For use in this assay, proteins are combined with a solid or semi-solid, biocompatible carrier, such as a polymer pellet. Angiogenesis is followed microscopically. Vascular growth into the corneal stroma can be detected in about 10 days.

Angiogenic activity can also be tested in the hampster cheek pouch assay (Höckel et al., Arch. Surg. 128:423-429, 1993). A test substance is injected subcutaneiously into the cheek pouch, and after five days the pouch is examined under low magnification to determine the extent of neovascularization. Tissue sections can also be examined histologically.

Induction of vascular permeability is measured in assays designed to detect leakage of protein from the vasculature of a test animal (e.g., mouse or guinea pig) after administration of a test compound (Miles and Miles, *J. Physiol.* 118:228-257, 1952; Feng et al., *J. Exp. Med.* 183:1981-1986, 1996).

Wound-healing models include the linear skin incision model of Mustoe et al. (Science 237:1333, 1987). In a typical procedure, a 6-cm incision is made in the dorsal pelt of an adult rat, then closed with wound clips. Test substances and controls (in solution, gel, or powder form) are applied before primary closure. It is preferred to limit administration to a single application, although additional applications can be made on succeeding days by careful injection at several sites under the incision. Wound breaking strength is evaluated between 3 and 21 days post wounding. In a second model, multiple, small, full-thickness excisions are made on the ear of a rabbit. The cartilage in the ear splints the wound, removing the variable of wound contraction from the evaluation of closure. Experimental treatments and controls are applied. The geometry and anatomy of the wound site allow for reliable quantification of cell ingrowth and epithelial migration, as well as quantitative analysis of the biochemistry of the wounds (e.g., collagen content). See, Mustoe et al., J. Clin. Invest. 87:694, 1991. The rabbit ear model can be modified to create an ischemic wound environment, which more closely resembles the clinical situation (Ahn et al., Ann. Plast. Surg. 24:17, 1990). Within a third model, healing of partial-thickness skin wounds in pigs or guinea pigs is evaluated (LeGrand et al., Growth Factors 8:307, 1993). Experimental

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treatments are applied daily on or under dressings. Seven days after wounding, granulation tissue thickness is determined. This model is preferred for dose-response studies, as it is more quantitative than other in vivo models of wound healing. A full thickness excision model can also be employed. Within this model, the epidermis and dermis are removed down to the panniculus carnosum in rodents or the subcutaneous fat in pigs. Experimental treatments are applied topically on or under a dressing, and can be applied daily if desired. The wound closes by a combination of contraction and cell ingrowth and proliferation. Measurable endpoints include time to wound closure, histologic score, and biochemical parameters of wound tissue. Impaired wound healing models are also known in the art (e.g., Cromack et al., Surgery 113:36, 1993; Pierce et al., Proc. Natl. Acad. Sci. USA 86:2229, 1989; Greenhalgh et al., Amer. J. Pathol. 136:1235, 1990). Delay or prolongation of the wound healing process can be induced pharmacologically by treatment with steroids, irradiation of the wound site, or by concomitant disease states (e.g., diabetes). Linear incisions or full-thickness excisions are most commonly used as the experimental wound. Endpoints are as disclosed above for each type of wound. Subcutaneous implants can be used to assess compounds acting in the early stages of wound healing (Broadley et al., Lab. Invest. 61:571, 1985; Sprugel et al., Amer. J. Pathol. 129: 601, 1987). Implants are prepared in a porous, relatively non-inflammatory container (e.g., polyethylene sponges or expanded polytetrafluoroethylene implants filled with bovine collagen) and placed subcutaneously in mice or rats. The interior of the implant is empty of cells, producing a "wound space" that is well-defined and separable from the preexisting tissue. This arrangement allows the assessment of cell influx and cell type as well as the measurement of vasculogenesis/angiogenesis and extracellular matrix production.

Inhibition of tumor metastasis can be assessed in mice into which cancerous cells or tumor tissue have been introduced by implantation or injection (e.g., Brown, *Advan. Enzyme Regul.* 35:293-301, 1995; Conway et al., *Clin. Exp. Metastasis* 14:115-124, 1996).

Effects on fibrinolysis can be measured in a rat model wherein the enzyme batroxobin and radiolabeled fibrinogen are administered to test animals. Inhibition of fibrinogen activation by a test compound is seen as a reduction in the circulating level of the label as compared to animals not receiving the test compound. See, Lenfors and Gustafsson, *Semin. Thromb. Hemost.* 22:335-342, 1996.

The invention further provides polypeptides that comprise an epitopebearing portion of a protein as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 436. An "epitope" is a region of a protein to which an antibody can bind. See, for example, Geysen et al., *Proc. Natl. Acad. Sci. USA* <u>81</u>:3998-4002, 1984.

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Epitopes can be linear or conformational, the latter being composed of discontinuous regions of the protein that form an epitope upon folding of the protein. Linear epitopes are generally at least 6 amino acid residues in length. Relatively short synthetic peptides that mimic part of a protein sequence are routinely capable of eliciting an antiserum that reacts with the partially mimicked protein. See, for example, Sutcliffe et al., Science 219:660-666, 1983. Antibodies that recognize short, linear epitopes are particularly useful in analytic and diagnostic applications that employ denatured protein, such as Western blotting (Tobin, Proc. Natl. Acad. Sci. USA 76:4350-4356, 1979). Antibodies to short peptides may also recognize proteins in native conformation and will thus be useful for monitoring protein expression and protein isolation, and in detecting proteins in solution, such as by ELISA or in immunoprecipitation studies.

Antigenic, epitope-bearing polypeptides of the present invention are useful for raising antibodies, including monoclonal antibodies, that specifically bind to the corresponding protein. Antigenic, epitope-bearing polypeptides contain a sequence of at least six, preferably at least nine, more preferably from 15 to about 30 contiguous amino acid residues of a protein. Within certain embodiments of the invention, the polypeptides comprise 40, 50, 100, or more contiguous residues of a protein as shown in SEQ ID NO:M, up to the entire predicted mature protein or the primary translation product. It is preferred that the amino acid sequence of the epitope-bearing polypeptide is selected to provide substantial solubility in aqueous solvents, that is the sequence includes relatively hydrophilic residues, and hydrophobic residues are substantially avoided. Table 10 lists preferred hexapeptides for use as antigens. Within Table 10, each the amino termini of the hexapeptides are specified. Those skilled in the art will recognize that longer polypeptides comprising these hexapeptides can also be used and will often be preferred.

		<u>Ta</u>	<u>ble 10</u>		
<u>Protein</u>		Hexa	peptide N	<u>-termini</u>	
AFP210015	389	405	97	388	359
AFP170681	51	334	113	49	140
AFP413680	221	207	220	206	198
AFP483037	219	218	82	216	215
AFP230872	189	188	73	156	68
AFP178828	211	210	209	208	207
AFP200134	150	149	146	132	145
AFP195796	99	97	111	208	240

AFP477303	64	126	63	54	112
AFP354334	269	268	267	266	265
AFP250287	34	33	48	2	143
AFP177000	133	132	104	37	68
AFP278176	234	145	,284	91	291
AFP202885	134	244	170	133	243
AFP221312	31	29	28	51	43
AFP239757	329	200	556	107	328
AFP226311	293	74	250	86	184
AFP305901	340	194	451	192	120
AFP325549	293	74	250	86	184
AFP81988	151	167	147	165	173
AFP199200	150	149	148	92	147
AFP290395	31	29	28	329	326
AFP212675	67	66	65	204	396
AFP326051	49	56	. 23	78	95
AFP512441	94	93	41	39	38
AFP55098	140	34	139	120	32
AFP169796	177	173	156	32	155
AFP280706	33	54	32	31	53
AFP383165	25	82	52	24	178
AFP195467	113	112	71	2	80
AFP134225	114	280	113	455	417
AFP261193	120	66	65	85	119
AFP324422	147	145	66	65	85 .
AFP374312	125	124	79	123	77
AFP258118	64	63	116	115	62
AFP74517	1	72	124	123	22
AFP254653	134	36	62	14	23
AFP108666	79	76	74	49	48
AFP8766	140	34	139	120	298
AFP397185	265	35	264	34	48
AFP195042	192	535	191	259	533
AFP310695	49	75	190	5	94
AFP70022	38	64	179	83	37
AFP121670	184	183	121	118	182
AFP345861	151	89	75	135	149

AFP395942	60	14	59	13	21
AFP170291	144	72	56	55	63
AFP297548	145	73	57	56	64
AFP188135	152	148	158	147	144
AFP302388	478	431	416	414	429
AFP263430	92	23	64	91	110
AFP201273	373	384	163	372	44
AFP98983	3	2	35	34	32
AFP581958	71	66	80	26	25
AFP404202	1	31	115	30	92
AFP207203	427	258	204	426	48
AFP220790	139	92	51	187	91
AFP536326	87	146	105	73	103
AFP257473	270	205	203	245	244
AFP248380	283	62	54	272	100
AFP276202	50	48	35	46	33
AFP227568	199	23	238	363	224
AFP229039	226	91	116	161	225
AFP176297	261	382	183	119	182
AFP356885	622	45	525	175	466
AFP226938	118	108	117	79	107
AFP138504	77	255	75	254	292
AFP359196	4	76	3	2	37
AFP501809	141	139	9	169	2
AFP152733	258	204	48	47	257
AFP541394	31	29	28	235	232
AFP243183	272	110	106	3	2
AFP80739	398	397	224	223	155
AFP361806	4	78	139	3	76
AFP483930	107	124	123	88	45
AFP257336	124	42	122	182	158
AFP195800	40	39	65	38	96
AFP179530	57	251	249	315	55
AFP279267	106	62	216	187	59
AFP299766	127	168	165	29	126
AFP244615	171	196	326	255	179
AFP325761	138	137	2	144	109

AFP226024	79	317	159	140	45
AFP257094	71	116	115	3	144
AFP197103	200	198	215	195	177
AFP271855	92	44	42	18	27
AFP324816	9	252	120	8	63
AFP407963	202	201	156	200	155
AFP369635	98	398	255	97	254
AFP93743	4	254	3	294	293
AFP243230	28	129	128	127	44
AFP169316	294	170	293	36	157
AFP130852	82	59	117	145	66
AFP194191	363	112	271	69	267
AFP213472	103	102	69 ·	2	37
AFP360430	177	75	183	74	130
AFP491309	107	106	69	2	37
AFP193428	129	87	343	60	128
AFP366534	72	4	2	59	39
AFP22706	229	227	65	64	188
AFP389012	216	27	289	34	17
AFP137186	2	1	182	216	43
AFP127023	86	56	131	178	55
AFP389687	. 57	56	117	370	369
AFP293220	186	194	105	146	182
AFP425535	264	181	163	370	149
AFP301494	159	4	2	84	25
AFP345421	500	592	639	652	849
AFP216667	92	435	329	422	47
AFP247951	27	34	33	25	94
AFP4464	365	363	362	55	209
AFP561930	108	107	104	52	66
AFP192851	300	276	299	298	496
AFP252759	311	310	64	21	157
AFP199044	143	2	209	206	125
AFP357958	167	338	165	324	362
AFP117501	135	87	362	86	418
AFP194554	318	170	54	105	169
AFP371069	332	1	283	365	279

AFP313600	341	340	240	48	176
AFP262739	25	24	142	23	207
AFP180730	58	37	30	27	36
AFP287227	596	. 592	591	374	525
AFP75785	128	127	136	99	71
AFP174843	152	323	150	309	347
AFP250422	100	140	99	138	182
AFP198645	145	144	143	64	56
AFP238111	123	50	20	137	35
AFP460626	153	151	71	150	70
AFP271081	68	112	. 39	202	67
AFP277752	109	106	220	238	92
AFP291338	347	342	97	362	339
AFP551038	134	131	186	130	173
AFP301579	105	153	130	152	67
AFP266188	121	235	61	180	120
AFP275580	193	77	192	2	148
AFP298054	148	234	146	233	144
AFP348226	148	103	85	309	59
AFP349106	208	118	117	207	116
AFP288248	376	342	340	339	312
AFP436476	18	39	139	38	99
AFP352125	53	59	163	142	104
AFP62060	247	187	73	426	72
AFP236718	100	99	249	248	184
AFP75775	201	90	239	173	199
AFP407487	148	103	85	59	58
AFP280451	141	294	6	209	139
AFP11675	58	56	90	64	89
AFP348656	160	159	158	103	149
AFP277451	118	2	1	146	241
AFP287436	53	59	223	142	104
AFP116043	212	239	138	186	183
AFP138740	264	263	31	72	232
AFP15192	47	46	216	85	212
AFP169968	64	117	63	2	81
AFP173341	65	64	102	101	100

AFP17588	43	42	2	41	1
AFP176427	311	290	308	155	288
AFP192633	58	56	162	349	44
AFP193013	47	90	87	46	68
AFP193881	274	295	402	273	292
AFP195562	274	295	339	473	273
AFP199922	57	55	74	180	50
AFP204736	89	58	43	28	23
AFP206179	74	80	73	71	70
AFP221877	32	31	30	50	75
AFP222758	44	43	75	42	19
AFP227032	47	55	46	65	54
AFP229269	147	127	146	63	60
AFP232213	44	41	28	27	40
AFP237679	2	1	34	58	55
AFP249599	48	47	45	43	42
AFP275215	82	80	70	2	55
AFP290397	149	148	2	1	29
AFP306591	45	44	84	83	65
AFP310297	23	31	37	47	30
AFP314720	47	44	26	25	23
AFP318671	55	54	51	64	63
AFP323575	75	73	72	70	18
AFP327160	37	68	47	67	96
AFP329002	78	77	76	75	74
AFP345415	41	40	133	106	39
AFP347179	30	4	29	86	177
AFP359138	77	2	76	75	74
AFP365372	13	1	62	69	79
AFP367284	61	60	36	5	59
AFP372822	49	48	25	8	24
AFP374595	154	153	165	3	56
AFP375952	36	35	53	52	69
AFP382913	67	32	30	20	66
AFP389184	24	31	78	30	39
AFP404208	69	68	67	39	36
AFP404279	81	31	72	30	62

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AFP409112	97	96	56	94	55
AFP413111	65	85	96	64	94
AFP415635	35	26	25	34	32
AFP421092	27	1	46	57	35
AFP436666	5	95	59	4	58
AFP448623	14				
AFP454192	106	104	83	114	112
AFP49026	49	104	76 ·	48	138
AFP51688	51	86	50	85	43
AFP525341	18	17	16	79	14
AFP545268	65	64	75	21	74
AFP592620	22	21	29	20	28
AFP62197	134	84	133	20	104
AFP68229	161	171	192	170	232
AFP71288	67	49	65	48	46
AFP77851	123	121	33	103	53
AFP81957	89	66	63	25	40
AFP85168	61	31	39	27	46

As used herein, the term "antibodies" includes polyclonal antibodies, monoclonal antibodies, antigen-binding fragments thereof such as F(ab')₂ and Fab fragments, single chain antibodies, and the like, including genetically engineered antibodies. Non-human antibodies can be humanized by grafting only non-human CDRs onto human framework and constant regions, or by incorporating the entire non-human variable domains (optionally "cloaking" them with a human-like surface by replacement of exposed residues, wherein the result is a "veneered" antibody). In some instances, humanized antibodies may retain non-human residues within the human variable region framework domains to enhance proper binding characteristics. Through humanizing antibodies, biological half-life may be increased, and the potential for adverse immune reactions upon administration to humans is reduced. One skilled in the art can generate humanized antibodies with specific and different constant domains (i.e., different Ig subclasses) to facilitate or inhibit various immune functions associated with particular antibody constant domains.

Alternative techniques for generating or selecting antibodies useful herein include *in vitro* exposure of lymphocytes to an immunogenic polypeptide, and selection of antibody display libraries in phage or similar vectors (for instance, through use of an immobilized or labeled polypeptide). Human antibodies can be produced in

transgenic, non-human animals that have been engineered to contain human immunoglobulin genes as disclosed in WIPO Publication WO 98/24893. It is preferred that the endogenous immunoglobulin genes in these animals be inactivated or eliminated, such as by homologous recombination.

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Antibodies are defined to be specifically binding if they bind to a target polypeptide with an affinity at least 10-fold greater than the binding affinity to control (non-target) polypeptide. It is preferred that the antibodies exhibit a binding affinity (K_a) of 10^6 M⁻¹ or greater, preferably 10^7 M⁻¹ or greater, more preferably 10^8 M⁻¹ or greater, and most preferably 10^9 M⁻¹ or greater. The affinity of a monoclonal antibody can be readily determined by one of ordinary skill in the art (see, for example, Scatchard, *Ann. NY Acad. Sci.* <u>51</u>: 660-672, 1949).

Methods for preparing polyclonal and monoclonal antibodies are well known in the art (see for example, Hurrell, J. G. R., Ed., Monoclonal Hybridoma Antibodies: Techniques and Applications, CRC Press, Inc., Boca Raton, FL, 1982). As would be evident to one of ordinary skill in the art, polyclonal antibodies can be generated from a variety of warm-blooded animals such as horses, cows, goats, sheep, dogs, chickens, rabbits, mice, and rats. The immunogenicity of a polypeptide immunogen may be increased through the use of an adjuvant such as alum (aluminum hydroxide) or Freund's complete or incomplete adjuvant. Polypeptides useful for immunization also include fusion polypeptides, such as fusions of a polypeptide of interest or a portion thereof with an immunoglobulin polypeptide or with maltose binding protein. The polypeptide immunogen may be a full-length molecule or a portion thereof. If the polypeptide portion is "hapten-like", such portion may be advantageously joined or linked to a macromolecular carrier (such as keyhole limpet hemocyanin (KLH), bovine serum albumin (BSA) or tetanus toxoid) for immunization.

A variety of assays known to those skilled in the art can be utilized to detect antibodies that specifically bind to a polypeptide of interest. Exemplary assays are described in detail in *Antibodies: A Laboratory Manual*, Harlow and Lane (Eds.), Cold Spring Harbor Laboratory Press, 1988. Representative examples of such assays include concurrent immunoelectrophoresis, radio-immunoassays, radio-immunoprecipitations, enzyme-linked immunosorbent assays (ELISA), dot blot assays, Western blot assays, inhibition or competition assays, and sandwich assays.

Antibodies can be used, for example, to isolate target polypeptides by affinity purification, for diagnostic assays for determining circulating or localized levels of target polypeptides, for tissue typing, for cell sorting, for screening expression libraries; for generating anti-idiotypic antibodies, and as neutralizing antibodies or as antagonists to block protein activity *in vitro* and *in vivo*.

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The present invention also provides reagents for use in diagnostic and therapeutic applications. Such reagents include polynucleotide probes and primers; antibodies, including antibody fragments, single-chain antibodies, and other genetically engineered forms; soluble receptors and other polypeptide binding partners; and the proteins of the invention themselves, including fragments thereof. Those skilled in the art will recognize that diagnostic reagents will commonly be labeled to provide a detectable signal or other second function. Thus, polypeptides, antibodies, receptors, and other binding partners disclosed herein can be directly or indirectly conjugated to drugs, toxins, radionuclides, enzymes, enzyme substrates, cofactors, inhibitors, fluorescent markers, chemiluminescent markers, magnetic particles, and the like, and these conjugates used for in vivo diagnostic or therapeutic applications. Cytotoxic molecules, for example, can be directly or indirectly attached to the binding partner (e.g., by chemical coupling or as a fusion protein), and include bacterial or plant toxins (e.g., diphtheria toxin, Pseudomonas exotoxin, ricin, saporin, abrin, and the like); therapeutic radionuclides (e.g., iodine-131, rhenium-188 or yttrium-90) which can be directly attached to a polypeptide or antibody or indirectly attached through means of a chelating moiety; and cytotoxic drugs (e.g., adriamycin). Methods for preparing labeled reagents are known in the art. Within an alternative embodiment, the detectable signal or other function can be provided by a second member of a complement-anticomplement pair, which second member binds to the diagnostic reagent. For example, a first (unlabeled) antibody can be used to bind to a cell-surface polypeptide, after which a second, labeled antibody which binds to the first antibody is added. Other complement-anticomplement pairs are known in the art and include biotin/streptavidin.

Diagnostic reagents as disclosed herein can be used *in vivo* or *in vitro*. In vitro diagnostic assays include assays of tissue and fluid samples. Assays for protein in serum, for example, may be used to detect metabolic abnormalities characterized by over- or under-production of the protein, such as cancers, immune system abnormalities, infections, organ failure, metabolic imbalances, inborn errors of metabolism and other disease states. Proteins of the present invention can also be used in the detection of circulating autoantibodies, which are indicative of autoimmune disorders. Those skilled in the art will recognize that conditions related to protein underexpression or overexpression may be amenable to treatment by therapeutic manipulation of the relevant protein level(s). Proteins in serum can be quantitated by known methods known in the art, which include the use of antibodies in a variety of formats. Non-antibody binding partners, such as ligand-binding receptor fragments (commonly referred to as "soluble receptors") can also be used.

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In general, diagnostic methods employing oligonucleotide probes or primers comprise the steps of (a) obtaining a genetic sample from a patient; (b) incubating the genetic sample with an oligonucleotide probe or primer as disclosed above, under conditions wherein the probe or primer will hybridize to a complementary polynucleotide sequence, to produce a first reaction product; and (c) comparing the first reaction product to a control reaction product. A difference between the first reaction product and the control reaction product is indicative of a genetic abnormality in the patient. Genetic samples for use within such methods include genomic DNA, cDNA, and RNA. Suitable assay methods in this regard include molecular genetic techniques known to those in the art, such as restriction fragment length polymorphism (RFLP) analysis, short tandem repeat (STR) analysis employing PCR techniques, ligation chain reaction (Barany, PCR Methods and Applications 1:5-16, 1991), ribonuclease protection assays, and other genetic linkage analysis techniques known in the art (Sambrook et al., ibid.; Ausubel et. al., ibid.; A.J. Marian, Chest 108:255-65, 1995). Ribonuclease protection assays (see, e.g., Ausubel et al., ibid., ch. 4) comprise the hybridization of an RNA probe to a patient RNA sample, after which the reaction product (RNA-RNA hybrid) is exposed to RNase. Hybridized regions of the RNA are protected from digestion. Within PCR assays, a patient genetic sample is incubated with a pair of oligonucleotide primers, and the region between the primers is amplified and recovered. Changes in size, amount, or sequence of recovered product are indicative of mutations in the patient. Another PCR-based technique that can be employed is single strand conformational polymorphism (SSCP) analysis (Hayashi, PCR Methods and Applications 1:34-38, 1991). Chromosomal localization data can be used to correlate AFP gene locations with known genetic disorders using, for example, the OMIMTM Database, **Johns** Hopkins University, 2000 (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM).

Relative chromosomal sublocalization shown in Table 11 was determined using the Draft Human Genome Browser (Kent, J., University of California Santa Cruz, http://genome.ucsc.edu/goldenPath/hgTracks.html) displaying the draft assembly of the July 17, 2000 version of the human genome. Table 11 also correlates AFP sequences with corresponding sequences in public databases by GenBank Accession Number, source clone ID number, and EST accession number. Also see Table 5, above.

			T	Table 11			
AFP	GenBank Acc. No.	Source Clone ID No.	EST Acc. No.	Ğ.	Band	Start	Stop
AFP127023	AP001155	RP11-594B10	*	- 18 - 18	18a12	35729370	35952786
AFP138504	AP001931	RP11-691N7	*	=	11p11.11	53438038	53888802
AFP138740	AC024059	RP11-79j21	AW580814	15	15q22.1	58185489	58481462
AFP138740	*	*	AW580814	15		58258653	58308652
AFP177000	AL118506	RP4-591C20	*	20	20q12	48950838	49160243
AFP178828	AC007686	CTD-2289B16;RP11-	*	14	14q23.3	62132030	62313415
000000		116N21;RP11-7F17					
AFP1/9530	AC011475	CTC-539A10	- * -	12	12q12	41234876	41456630
AFP188135	AC013740	*		6	9q31.2	91150313	91361876
AFP194554	AC024888	RP11-901L	*	16	16q22.1	71944378	72167142
AFP199044	AC012180	RP11-31110	*	16	16911.2	44574019	44904017
AFP199200	CNS01DV7	BAC-R-1070N10	*	14		82330266	82541053
AFP229269	AL161670	BAC-R-804M7	*	14	14q21.3	46135365	46299284
AFP236718	AC010319	CTD-2521M24	*	61	19p13.3	4839920	5087628
AFP237679	60L69Z	*	*	4	4p16.3	4521455	4544888
AFP244615	*	*	AI494556;AW85055	3	3q13.12	116466893	116517043
AFP240500	AT 157714	DD11 5/11113	*				
AFP250422	AC012046	PD11 317D17	*	- -	1922-23.3	161893354	162136704
A FD262730	A COOK 804	11-312F 12		01	10922.1	81289799	81650062
A EBOTEGOO	AC003004	#KFN.204_B_14		-	17q23.3	64245127	64365313
AFP277451	AC010//3	*	×	3	3q21.3	141329005	141513510
AFP27027	AC055822	KP11-707M3	*	∞	8q13.3	75395740	75583383
AFP2/926/	*	*	AI566086	10	10q11.1	52859924	52861338
AFP280451	AL133355	RP11-541N10	*	10	10q24.32	115276306	115467187
AFP290397	*	*	AA421069	15	15q15,3	48427462	48427830
AFP293220	AC012476	RP11-532F12	*	15	15p11.1	17263661	17480097
AFP297548	*	*	W52728	11	11q11	57918740	57927327
AFP306591	AQ079258	2366B9	AW118928	9	6p22.3	19812023	19812791
AFP313600	AC005037	NH0469M07	*	2	2q33.1	205320800	205511307
AFP324816	AC011687	RP11-15120	*	2	2p21	49054619	49249783
AFP323/61	AC012485	RP11-5024	*	2	2p24.3	17554756	17765537

AL132639	BAC-R-407N17	AI525611	14	145111	10050402	20152250
AC015936	1	*	17	17021 2	44087441	44786504
AC025740	 -	*	12	12024 23	125918909	176134148
AL022240	3.28E+21	*	-	1012-21 2	138667522	138765140
	*	AI253088		11023 3	128134250	128134580
	*	AI741157	19	16p13.3	3479999	3500834
AC004235	*	*	91	16p13.3	4189155	4222465
	*	AI133727	7		142961410	143641730
	*	AI341602	4	4p16.3	1512179	1514256
AC006942	cosmid-R31181	*	19	19q13.33	59897688	59940397
	*	AI814257	8	8p21.3	18993217	19003942
	*	AI140615	5	5933.1	173540737	173547400
AC009131	RP11-502K10	*	91	16922.1	70222075	70471703
AC008686	CTB-5E10	*	19	19p13.13	16491516	16677574
	*	AW583171	9	6p21.1	50554924	50564907
AL138695	RP11-342J4	*	13	13021.1	60450247	60714738
AL136221	RP11-391H12	*	13	13934	108494503	108794286
	*	AA493506	9	6022.33	137477811	137478427
HS1056L3	RP5-1056L3	*	11	1p35.1-36.13	*	*
AC067942	RP11-791G16	*	4	4q21.22	77419530	77633569

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If a mammal has an insufficiency of a protein of interest (due to, for example, a mutated or absent gene), the corresponding wild-type gene can be introduced into the cells of the mammal. In one embodiment, a gene encoding a protein of interest is introduced into the animal using a viral vector. Such vectors include an attenuated or defective DNA virus, such as, but not limited to, herpes simplex virus (HSV), papillomavirus, Epstein Barr virus (EBV), adenovirus, adenoassociated virus (AAV), and the like. Defective viruses, which entirely or almost entirely lack viral genes, are preferred. A defective virus is not infective after introduction into a cell. Use of defective viral vectors allows for administration to cells in a specific, localized area, without concern that the vector can infect other cells. Examples of particular vectors include, but are not limited to, a defective herpes simplex virus 1 (HSV1) vector (Kaplitt et al., Molec. Cell. Neurosci. 2:320-30, 1991); an attenuated adenovirus vector, such as the vector described by Stratford-Perricaudet et al. (J. Clin. Invest. 90:626-30, 1992); and a defective adeno-associated virus vector (Samulski et al., J. Virol. 61:3096-101, 1987; Samulski et al., J. Virol. 63:3822-28, 1989).

Within another embodiment, a gene of interest is introducted into an animal by liposome-mediated transfection ("lipofection") essentially as disclosed above. Lipofection can be used to introduce exogenous genes into specific organs.

A gene of interest can also be introduced into an animal for gene therapy as a naked DNA plasmid using the methods disclosed above.

In another embodiment, polypeptide-toxin fusion proteins or antibody/fragment-toxin fusion proteins may be used for targeted cell or tissue inhibition or ablation, such as in cancer therapy. Of particular interest in this regard are conjugates of an AFP protein and a cytotoxin, which can be used to target the cytotoxin to a tumor or other tissue that is undergoing undesired angiogenesis or neovascularization.

In another embodiment, AFP-cytokine fusion proteins or antibody/fragment-cytokine fusion proteins may be used for enhancing *in vitro* cytotoxicity (for instance, that mediated by monoclonal antibodies against tumor targets) and for enhancing *in vivo* killing of target tissues (for example, blood and bone marrow cancers). See, generally, Hornick et al., *Blood* 89:4437-4447, 1997). In general, cytokines are toxic if administered systemically. The described fusion proteins enable targeting of a cytokine to a desired site of action, such as a cell having binding sites for an AFP protein, thereby providing an elevated local concentration of cytokine. Polypeptides, antibodies, or receptors target an undesirable cell or tissue

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(e.g., a tumor), and the fused cytokine mediates improved target cell lysis by effector cells. Suitable cytokines for this purpose include, for example, interleukin-2 and granulocyte-macrophage colony-stimulating factor (GM-CSF).

In another embodiment, polypeptide-toxin fusion proteins or other binding partner-linked toxins may be used for targeted cell or tissue inhibition or ablation (for instance, to treat cancer cells or tissues). Target cells (i.e., those displaying a receptor for a polypeptide of interest) bind the polypeptide-toxin conjugate, which is then internalized, killing the cell. The effects of receptor-specific cell killing (target ablation) are revealed by changes in whole animal physiology or 10 through histological examination. Thus, ligand-dependent, receptor-directed cyotoxicity can be used to enhance understanding of the physiological significance of a protein ligand. A preferred such toxin is saporin. Mammalian cells have no receptor for saporin, which is non-toxic when it remains extracellular. Alternatively, if the polypeptide of interest has multiple functional domains (i.e., an activation domain or a ligand binding domain, plus a targeting domain), a fusion protein including only the targeting domain may be suitable for directing a detectable molecule, a cytotoxic molecule or a complementary molecule to a cell or tissue type of interest. In instances where the domain-only fusion protein includes a complementary molecule, the anticomplementary molecule can be conjugated to a detectable or cytotoxic molecule. Such domain-complementary molecule fusion proteins thus represent a generic targeting vehicle for cell- or tissue-specific delivery of generic anti-complementarydetectable/cytotoxic molecule conjugates.

The bioactive conjugates described herein can be intravenously, intraarterially or intraductally, or may be introduced locally at the intended site of action.

For pharmaceutical use, the proteins of the present invention are formulated according to conventional methods. Routes of delivery include topical, mucosal, and parenteral, the latter including intravenous and subcutaneous delivery. Intravenous administration will be by bolus injection or infusion over a typical period of one to several hours. In general, pharmaceutical formulations will include a protein of the present invention in combination with a pharmaceutically acceptable vehicle, such as saline, buffered saline, 5% dextrose in water or the like. Formulations may further include one or more excipients, diluents, fillers, emulsifiers, preservatives, solubilizers, buffering agents, wetting agents, stabilizers, colorings, penetration enhancers, albumin to prevent protein loss on vial surfaces, etc. Topical formulations are typically provided as liquids, ointments, salves, gels, emulsions and the like. Methods of formulation are well known in the art and are disclosed, for example, in

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Remington: The Science and Practice of Pharmacy, Gennaro, ed., Mack Publishing Co., Easton, PA, 19th ed., 1995. Therapeutic doses will be determined by the clinician according to accepted standards, taking into account the nature and severity of the condition to be treated, patient traits, etc. Proteins of the present invention will generally be formulated to provide a dose of from 0.01 µg to 100 mg per kg patient weight per day, more commonly from 0.1 µg to 10 mg/kg/day, still more commonly from 0.1 µg to 1.0 mg/kg/day. Determination of dose is within the level of ordinary skill in the art. The proteins may be administered for acute treatment, over one week or less, often over a period of one to three days or may be used in chronic treatment, over several months or years. In general, a therapeutically effective amount is an amount sufficient to produce a clinically significant change in the targetted condition.

Within the laboratory research field, the proteins of the present invention can be used as molecular weight standards, or as standards in the analysis of cell phenotype, and as reagents for the study of cells, receptors, and other binding molecules. Such reagents will generally further comprise a second moiety, such as a label, binding partner, or toxin, that facilitates the detection of the protein when bound to its target. Many such systems are known in the art and are summarized above. Receptors and other cell-surface binding sites for proteins of the present invention can be identified by exposing a population of cells to a labelled protein under physiologic conditions, whereby the protein binds to the surface of the cell. Cells bearing receptors for a protein of interest can also be identified using the protein joined to a toxin, whereby receptor-bearing cells are killed by the toxin.

AFP proteins and antagonists thereof can be used as standards in assays of protein and protein inhibitors in both clinical and research settings. Such assays can comprise any of a number of standard formats, include radioreceptor assays and ELISAs. Protein standards can be prepared in labeled form using a radioisotope, enzyme, fluorophore, or other compound that produces a detectable signal. The proteins can be packaged in kit form, such kits comprising one or more vials containing the AFP protein and, optionally, a diluent, an antibody, a labeled binding protein, etc. Assay kits can be used in the research laboratory to detect protein and inhibitor activities produced by cultured cells or test animals.

Proteins of the present invention may also be used as protein and amino acid supplements, including hydrolysates. Specific uses in this regard include use as animal feed supplements and as cell culture components. Proteins rich in a particular amino acid can be used as a source of that amino acid.

Polynucleotides and polypeptides of the present invention will additionally find use as educational tools as a laboratory practicum kits for courses

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related to genetics and molecular biology, protein chemistry and antibody production and analysis. Due to their unique polynucleotide and polypeptide sequences, molecules of AFP protein or polynucleotide can be used as standards or as "unknowns" for testing purposes. For example, AFP polynucleotides can be used as aids in teaching students how to prepare expression constructs for bacterial, viral, and/or mammalian expression, including fusion constructs, wherein an AFP polynucleotide is the gene to be expressed; for determining the restriction endonuclease cleavage sites of the polynucleotides (which can be determined from the sequence using conventional computer software, such as MapDrawTM (DNASTAR, Madison, WI)); determining mRNA and DNA localization of AFP polynucleotides in tissues (e.g., by Northern and Southern blotting as well as polymerase chain reaction); and for identifying related polynucleotides and polypeptides by nucleic acid hybridization.

AFP polypeptides can be used educationally as aids to teach preparation of antibodies; identifying proteins by Western blotting; protein purification; determining the weight of expressed AFP polypeptides as a ratio to total protein expressed; identifying peptide cleavage sites; coupling amino and carboxyl terminal tags; amino acid sequence analysis, as well as, but not limited to monitoring biological activities of both the native and tagged protein (i.e., receptor binding, signal transduction, proliferation, and differentiation) in vitro and in vivo. AFP polypeptides can also be used to teach analytical skills such as mass spectrometry, circular dichroism to determine conformation, in particular the locations of the disulfide bonds, x-ray crystallography to determine the three-dimensional structure in atomic detail, nuclear magnetic resonance spectroscopy to reveal the structure of proteins in solution. For example, a kit containing an AFP protein can be given to the student to analyze. Since the amino acid sequence would be known by the professor, the protein can be given to the student as a test to determine the skills or develop the skills of the student, the teacher would then know whether or not the student has correctly analyzed the polypeptide. Since every polypeptide is unique, the educational utility of zcub5 would be unique unto itself.

Antibodies that bind specifically to an AFP polypeptide can be used as a teaching aid to instruct students how to prepare affinity chromatography columns to purify the cognate polypeptide, cloning and sequencing the polynucleotide that encodes an antibody and thus as a practicum for teaching a student how to design humanized antibodies. The AFP polynucleotide, polypeptide or antibody would then be packaged by reagent companies and sold to universities so that the students gain skill in art of molecular biology. Because each polynucleotide and protein is unique, each polynucleotide and protein creates unique challenges and learning experiences for

students in a lab practicum. Such educational kits containing an AFP polynucleotide, polypeptide or antibody are considered within the scope of the present invention.

The invention is further illustrated by the following non-limiting examples.

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EXAMPLES

Example 1

A protein of the present invention ("AFP") is produced in *E. coli* using a His₆ tag/maltose binding protein (MBP) double affinity fusion system as generally disclosed by Pryor and Leiting, *Prot. Expr. Pur.* 10:309-319, 1997. A thrombin cleavage site is placed at the junction between the affinity tag and AFP sequences.

The fusion construct is assembled in the vector pTAP98, which comprises sequences for replication and selection in *E. coli* and yeast, the *E. coli* tac promoter, and a unique Smal site just downstream of the MBP-His6-thrombin site coding sequences. The AFP cDNA is amplified by PCR using primers each comprising 40 bp of sequence homologous to vector sequence and 25 bp of sequence that anneals to the cDNA. The reaction is run using Taq DNA polymerase (Boehringer Mannheim, Indianapolis, IN) for 30 cycles of 94°C, 30 seconds; 60°C, 60 seconds; and 72°C, 60 seconds. One microgram of the resulting fragment is mixed with 100 ng of Smal-cut pTAP98, and the mixture is transformed into yeast to assemble the vector by homologous recombination (Oldenburg et al., *Nucl. Acids. Res.* 25:451-452, 1997). Ura⁺ transformants are selected.

Plasmid DNA is prepared from yeast transformants and transformed into *E. coli* MC1061. Pooled plasmid DNA is then prepared from the MC1061 transformants by the miniprep method after scraping an entire plate. Plasmid DNA is analyzed by restriction digestion.

E. coli strain BL21 is used for expression of AFP. Cells are transformed by electroporation and grown on minimal glucose plates containing casamino acids and ampicillin.

Protein expression is analyzed by gel electrophoresis. Cells are grown in liquid glucose media containing casamino acids and ampicillin. After one hour at 37°C, IPTG is added to a final concentration of 1mM, and the cells are grown for an additional 2-3 hours at 37°C. Cells are disrupted using glass beads, and extracts are prepared.

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Example 2

Larger scale cultures of AFP transformants are prepared by the method of Pryor and Leiting (ibid.). 100-ml cultures in minimal glucose media containing casamino acids and 100 µg/ml ampicillin are grown at 37°C in 500-ml baffled flasks to $OD_{600} \approx 0.5$. Cells are harvested by centrifugation and resuspended in 100 ml of the same media at room temperature. After 15 minutes, IPTG is added to 0.5 mM, and cultures are incubated at room temperature (ca. 22.5°C) for 16 to 20 hours with shaking at 125 rpm. The culture is harvested by centrifugation, and cell pellets are stored at -70°C.

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Example 3

For larger-scale protein preparation, 500-ml cultures of E. coli BL21 expressing the AFP-MBP-His6 fusion protein are prepared essentially as disclosed in Example 2. Cell pellets are resuspended in 100 ml of binding buffer (20 mM Tris, pH 7.58, 100 mM NaCl, 20 mM NaH₂PO₄, 0.4 mM 4-(2-Aminoethyl)-benzenesulfonyl fluoride hydrochloride [Pefabloc® SC; Boehringer-Mannheim], 2 µg/ml Leupeptin, 2 µg/ml Aprotinin). The cells are lysed in a French press at 30,000 psi, and the lysate is centrifuged at 18,000 x g for 45 minutes at 4°C to clarify it. Protein concentration is estimated by gel electrophoresis with a BSA standard.

20 . Recombinant AFP fusion protein is purified from the lysate by affinity chromatography. Immobilized cobalt resin (Talon® resin; Clontech Laboratories, Inc., Palo Alto, CA) is equilibrated in binding buffer. One ml of packed resin per 50 mg protein is combined with the clarified supernatant in a tube, and the tube is capped and sealed, then placed on a rocker overnight at 4°C. The resin is then pelleted by centrifugation at 4°C and washed three times with binding buffer. Protein is eluted with binding buffer containing 0.2 M imidazole. The resin and elution buffer are mixed for at least one hour at 4°C, the resin is pelleted, and the supernatant is removed. An aliquot is analyzed by gel electrophoresis, and concentration is estimated. Amylose resin is equilibrated in amylose binding buffer (20 mM Tris-HCl, pH 7.0, 100 mM NaCl, 10 mM EDTA) and combined with the supernatant from the Talon resin at a ratio of 2 mg fusion protein per ml of resin. Binding and washing steps are carried out as disclosed above. Protein is eluted with amylose binding buffer containing 10 mM maltose using as small a volume as possible to minimize the need for subsequent concentration. The eluted protein is analyzed by gel electrophoresis and staining with Coomassie blue using a BSA standard, and by Western blotting using an anti-MBP antibody.

Example 4

An expression plasmid containing all or part of a polynucleotide encoding AFP is constructed via homologous recombination. An AFP coding sequence comprising the ORF with 5' and 3' ends corresponding to the vector sequences flanking the insertion point is prepared by PCR. The primers for PCR each include from 5' to 3' end: 40 bp of flanking sequence from the vector and 17 bp corresponding to the amino or carboxyl termini from the open reading frame of AFP.

Ten µl of the 100 µl PCR reaction mixture is run on a 0.8% lowmelting-temperature agarose (SeaPlaque GTG®; FMC BioProducts, Rockland, ME) gel with 1 x TBE buffer for analysis. The remaining 90 µl of the reaction mixture is precipitated with the addition of 5 µl 1 M NaCl and 250 µl of absolute ethanol. The plasmid pZMP6, which has been cut with SmaI, is used for recombination with the PCR fragment. Plamid pZMP6 is a mammalian expression vector containing an expression cassette having the cytomegalovirus immediate early promoter, multiple restriction sites for insertion of coding sequences, a stop codon, and a human growth hormone terminator; an E. coli origin of replication; a mammalian selectable marker expression unit comprising an SV40 promoter, enhancer and origin of replication, a DHFR gene, and the SV40 terminator; and URA3 and CEN-ARS sequences required for selection and replication in S. cerevisiae. It was constructed from pZP9 (deposited at the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209, under Accession No. 98668) with the yeast genetic elements taken from pRS316 (available from the American Type Culture Collection, 10801 University Boulevard, Manassas, VA, under Accession No. 77145), an internal ribosome entry site (IRES) element from poliovirus, and the extracellular domain of CD8 truncated at the C-terminal end of the transmembrane domain.

One hundred microliters of competent yeast (S. cerevisiae) cells are independently combined with 10 μl of the various DNA mixtures from above and transferred to a 0.2-cm electroporation cuvette. The yeast/DNA mixtures are electropulsed using power supply (BioRad Laboratories, Hercules, CA) settings of 0.75 kV (5 kV/cm), ∞ ohms, 25 μF. To each cuvette is added 600 μl of 1.2 M sorbitol, and the yeast is plated in two 300-μl aliquots onto two URA-D plates (1.8% agar in 2% D-glucose, 0.67% yeast nitrogen base without amino acids, 0.056% -Ura -Trp -Thr powder [made by combining 4.0 g L-adenine, 3.0 g L-arginine, 5.0 g L-aspartic acid, 2.0 g L-histidine, 6.0 g L-isoleucine, 8.0 g L-leucine, 4.0 g L-lysine, 2.0 g L-methionine, 6.0 g L-phenylalanine, 5.0 g L-serine, 5.0 g L-tyrosine, and 6.0 g L-valine], and 0.5% 200X tryptophan, threonine solution [3.0% L-threonine, 0.8% L-tryptophan in H₂O]) and incubated at 30°C. After about 48 hours, the Ura⁺ yeast

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transformants from a single plate are resuspended in 1 ml H_2O and spun briefly to pellet the yeast cells. The cell pellet is resuspended in 1 ml of lysis buffer (2% Triton X-100, 1% SDS, 100 mM NaCl, 10 mM Tris, pH 8.0, 1 mM EDTA). Five hundred microliters of the lysis mixture is added to an Eppendorf tube containing 300 μ l acidwashed glass beads and 200 μ l phenol-chloroform, vortexed for 1 minute intervals two or three times, and spun for 5 minutes in an Eppendorf centrifuge at maximum speed. Three hundred microliters of the aqueous phase is transferred to a fresh tube, and the DNA is precipitated with 600 μ l ethanol (EtOH), followed by centrifugation for 10 minutes at 4°C. The DNA pellet is resuspended in 10 μ l H_2O .

Transformation of electrocompetent *E. coli* host cells (Electromax DH10BTM cells; obtained from Life Technologies, Inc., Gaithersburg, MD) is done with 0.5-2 ml yeast DNA prep and 40 μl of cells. The cells are electropulsed at 1.7 kV, 25 μF, and 400 ohms. Following electroporation, 1 ml SOC (2% BactoTM Tryptone (Difco, Detroit, MI), 0.5% yeast extract (Difco), 10 mM NaCl, 2.5 mM KCl, 10 mM MgCl₂, 10 mM MgSO₄, 20 mM glucose) is plated in 250-μl aliquots on four LB AMP plates (LB broth (Lennox), 1.8% BactoTM Agar (Difco), 100 mg/L Ampicillin).

Individual clones harboring the correct expression construct for AFP are identified by restriction digest to verify the presence of the AFP insert and to confirm that the various DNA sequences have been joined correctly to one another. The inserts of positive clones are subjected to sequence analysis. Larger scale plasmid DNA is isolated using a commercially available kit (QIAGEN Plasmid Maxi Kit, Qiagen, Valencia, CA) according to manufacturer's instructions. The correct construct is designated pZMP6/AFP.

Recombinant protein is produced in BHK cells transfected with pZMP6/AFP. BHK 570 cells (ATCC CRL-10314) are plated in 10-cm tissue culture dishes and allowed to grow to approximately 50 to 70% confluence overnight at 37°C, 5% CO₂, in DMEM/FBS media (DMEM, Gibco/BRL High Glucose; Life Technologies), 5% fetal bovine serum (Hyclone, Logan, UT), 1 mM L-glutamine (JRH Biosciences, Lenexa, KS), 1 mM sodium pyruvate (Life Technologies). The cells are then transfected with pZMP6/AFP by liposome-mediated transfection using a 3:1 (w/w) liposome formulation of the polycationic lipid 2,3-dioleyloxy-N-[2(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propaniminium-trifluoroacetate and the neutral lipid dioleoyl phosphatidylethanolamine in membrane-filtered water (LipofectamineTM Reagent; Life Technologies, Garithersburg, MD), in serum free (SF) media (DMEM supplemented with 10 mg/ml transferrin, 5 mg/ml insulin, 2 mg/ml fetuin, 1% L-glutamine and 1% sodium pyruvate). The plasmid is diluted into 15-ml tubes to a total final volume of 640 μl with SF media. 35 μl of the lipid mixture is

mixed with 605 μl of SF medium, and the resulting mixture is allowed to incubate approximately 30 minutes at room temperature. Five milliliters of SF media is then added to the DNA:lipid mixture. The cells are rinsed once with 5 ml of SF media, aspirated, and the DNA:lipid mixture is added. The cells are incubated at 37°C for five hours, then 6.4 ml of DMEM/10% FBS, 1% PSN media is added to each plate. The plates are incubated at 37°C overnight, and the DNA:lipid mixture is replaced with fresh 5% FBS/DMEM media the next day. On day 5 post-transfection, the cells are split into T-162 flasks in selection medium (DMEM + 5% FBS, 1% L-Gln, 1% NaPyr, 1 μM methotrexate). Approximately 10 days post-transfection, two 150-mm culture dishes of methotrexate-resistant colonies from each transfection are trypsinized, and the cells are pooled and plated into a T-162 flask and transferred to large-scale culture.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

We claim:

- 1. An isolated polypeptide comprising fifteen contiguous amino acid residues of a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422.
- 2. The isolated polypeptide of claim 1 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 3. The isolated polypeptide of claim 1 or claim 2 which is from 15 to 2235 amino acid residues in length.
- 4. The isolated polypeptide of claim 3 which is operably linked via a peptide bond or polypeptide linker to a second polypeptide selected from the group consisting of maltose binding protein, an immunoglobulin constant region, a polyhistidine tag, and a peptide as shown in SEQ ID NO:423.
- 5. The isolated polypeptide of any of claims 1-4 comprising at least 30 contiguous residues of SEQ ID NO:M.
- 6. The isolated polypeptide of any of claims 1-5 comprising at least 47 contiguous residues of SEQ ID NO:M.
- 7. An isolated, mature protein encoded by a sequence selected from the group consisting of SEQ ID NO:N, wherein N is an odd integer from 1 to 421.
- 8. The protein of claim 7 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 9. An isolated polynucleotide comprising a sequence of nucleotides as shown in SEQ ID NO:N, wherein N is an odd integer from 1 to 421.

- 10. The isolated polynucleotide of claim 9 wherein N is 5, 7, 11, 17, 23, 41, 47, 53, 65, 67, 69, 71, 89, 91, 95, 97, 101, 105, 109, 121, 133, 137, 139, 155, 157, 161, 163, 167, 173, 177, 179, 203, 205, 209, 223, 229, 233, 235, 239, 241, 251, 253, 257, 269, 271, 283, 285, 287, 293, 299, 301, 305, 311, 313, 323, 325, 337, 341, 343, 347, 349, 365, 367, 373, 377, 385, 387, 395, 397, 401, 407, 411, or 415.
- 11. An expression vector comprising the following operably linked elements:
 - a transcription promoter;
- a DNA segment encoding a polypeptide as shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422; and
 - a transcription terminator.
- 12. The expression vector of claim 11 wherein M is 6, 8, 12, 18, 24, 42, 48, 54, 66, 68, 70, 72, 90, 92, 96, 98, 102, 106, 110, 122, 134, 138, 140, 156, 158, 162, 164, 168, 174, 178, 180, 204, 206, 210, 224, 230, 234, 236, 240, 242, 252, 254, 258, 270, 272, 284, 286, 288, 294, 300, 302, 306, 312, 314, 324, 326, 338, 342, 344, 348, 350, 366, 368, 374, 378, 386, 388, 396, 398, 402, 408, 412, or 416.
- 13. A cultured cell comprising the expression vector of claim 11 or claim 12.
- 14. A method of producing a polypeptide comprising culturing the cell of claim 13 under conditions whereby said sequence of nucleotides is expressed, and recovering said polypeptide.
 - 15. A polypeptide produced by the method of claim 14.
- 16. An isolated polynucleotide encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide.
- 17. An expression vector comprising the following operably linked elements:

- a transcription promoter;
- a DNA segment encoding a fusion protein, said protein comprising a secretory peptide selected from the group consisting of secretory peptides shown in SEQ ID NO:M, wherein M is an even integer from 2 to 422, operably linked to a second polypeptide; and a transcription terminator.
- 18. A cultured cell comprising the expression vector of claim 17, wherein the cell expresses the DNA segment and produces the encoded fusion protein.
- 19. A method of producing a protein comprising culturing the cell of claim 18 under conditions whereby said DNA segment is expressed, and recovering said second polypeptide.
- 20. An antibody that specifically binds to a protein selected from of the group consisting of SEQ ID NO:M, wherein M is an even integer from 2 to 422.

1

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Trp	Lys 450	Gln	Leu	Ser	Leu	Pro 455	Gln	Gln	Glu	Ala	G1n 460	Lys	Ile	Phe	Lys
A1 a 465	Asn	His	Pro	Met	Asp 470	Ala	Glu	Val	Thr	Lys 475	Ala	Lys	Leu	Leu	G1y 480
Phe	Gly	Ser	Ala	Leu 485	Leu	Asp	Asn	Val	Asp 490	Pro	Asn	Pro	Glu	Asn. 495	
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Asp	Tyr 210	Gln	۷a٦	He	Ser	Asp 215		G1n	Thr	Pro	Lys 220	Lys	Asp	Glu	Ser	٠
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				aat Asn												144
				gta Val												192
				aga Arg												240

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						aat Asn							336
						cat His							384
						tat Tyr 135							432
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Asn	aag Lys 210		taa *									ı	636
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His	Arg 50	Thr	His	Val	Val	A1a 55	Arg	Lys	Met	Tyr	Lys 60	Ile	Leu	ı Asp	Leu	
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			100					105					110		Leu	
		115				His	120					125				
	130					Tyr 135					140					
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			180			Lys		185					190			
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cct Pro	ccg (Pro l	ccg (Pro	ccc (Pro l	cca Pro	cct Pro	ctg (Leu (gga Glv	ccc Pro	cat His	tcc Ser	aac Asn	cgg Ara	acc Thr	acc Thr	cca Pro	96

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															agt Ser	
						gcg Ala									cca Pro 80	24
						ccg Pro										28
						gtg Val										330
						ccc Pro										384
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Pro Glu Ser Ala Pro Gln Asn Gly Pro Ser Pro Met Ala Ala Leu Met 35 40 45

Ser Val Ala Asp Thr Leu Gly Thr Ala His Ser Pro Lys Asp Gly Ser 50 55 60

Ser Val His Ser Thr Thr Ala Ser Ala Arg Arg Asn Ser Ser Pro 65 70 75 80

Val Ser Pro Ala Ser Val Pro Gly Gln Arg Arg Leu Ala Ser Arg Asn 85 90 95

Gly Asp Leu Asn Leu Gln Val Ala Pro Pro Pro Pro Ser Ala His Pro 100 105 110

Gly Met Asp Gln Val His Pro Gln Asn Ile Pro Asp Ser Pro Met Ala 115 120 125

Asn Ser Gly Pro Leu Cys Cys Thr Ile Cys His Glu Arg Leu Glu Asp 130 135 140

Thr His Phe Val Gln Cys Pro Ser Val Pro Ser His Lys Phe Cys Phe 145 150 155 160

Pro Cys Ser Arg Glu Ser Ile Lys Ala Gln Gly Ala Thr Gly Glu Val

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Val Ser Phe Gln Gly Phe Ile Leu Gln Val Gly Ser Gly Ala Ala Ala
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Glu Pro Ser Arg Gly Thr Gly Ser Ser Gly Pro Ser Ser Gln His Pro
Leu Ser Gln Ala His Arg Gln Gly Asn Phe Val Asp Ile Val Asp Ala
Lys Leu Lys Ile Pro Val Ser Gly Ser Lys Ser Glu Gly Leu Leu Tyr
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                                105
Val His Ser Ser Arg Gly Gly Pro Phe Gln Arg Trp His Leu Asp Glu
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	Lys		gcg Ala								Ser						720
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gac Asp	ctc Leu	atc Ile	act Thr 100	Gly	ggc Gly	atc Ile	atc Ile	aca Thr 105	Glu	ctg Leu	ggg G1y	gto Val	ttt Phe 110	Ala	cct Pro	336
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_							_						acc Thr		-	480
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									-		_		ttc Phe 270			816
													gag Glu			864
tac	aaa	tat	gag	atc	tac	agc	pss	acc	ttc	tcc	caa	agc	tct	gac	ctc	912

Tyr	Lys 290	Cys	Glu	Val	Cys	Ser 295	Lys	Ala	Phe	Ser	Gln 300	Ser	Ser	Asp	Leu	
									gag Glu							960
•	_					-			tct Ser 330				-		_	1008
•					-				aag Lys	-					-	1056
-								_	cga Arg			_			-	1104
	-								tgc Cys							1152
									gtg Val							1200
									ttc Phe 410							1248
							-		gag G1u				-	_		1296
									tcg Ser							1344
									agc Ser							1392
acc	ttc	aat	cgc	tcc	tcc	act	ctc	atc	cag	cac	cag	cgc	tcc	cac	acg	1440

									35							
Thr 465		e Asr	ı Arg	ser Ser	Ser 470		Leu	ΙÌє	e Glr	His 475		n Arg	J Sei	his '	Thr 480	
ggo Gly	gag Glu	ı cgg ı Arg	ccc Pro	tac Tyr 485	Arg	tgc Cys	gcc	gtg Val	tgc Cys 490	Gly	aag Lys	1 990 Gly	tto Phe	tgc Cys 495	cgc Arg	1488
tcc Ser	tcc Ser	acg Thr	ctt Leu 500	Leu	cag Gln	cat His	cac His	cgg Arg 505	Val	cac	agt Ser	ggc	gag Glu 510	ı Arg	cct Pro	1536
			Asp										Ser		ctc Leu	1584
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Met 1	G1u	Arg	Glu	Ala 5	Leu	Pro	Trp	Gly	Leu 10	Glu	Pro	Gln	Asp	Val 15	Gln	
Ser	Ser	Asp	G1u 20	Met	Arg	Ser		G1u 25		Asn	Leu	Arg	Gly 30		Met	
Ser	Glu	Asn 35		Glu	Glu				Gln	Gln	Glu			Gly	Asp	
Tyr	G]ս 50		Glu	Glu	Ile			Gly	Leu	Glu	Pro 60	45 G1n	Ser	Pro	Gly	
Phe 65		Pro	Gln	Ser	Pro 70		Phe	G1u	Pro			Pro	Arg	Phe		
	Glu	Ser		Gly 85	Phe	Glu	Ser			75 Pro	Gly	Leu	Val		80 Pro	
Ser	Pro	Glu			Pro	Arg	Ser		90 Glu	Ser	Asp	Ser	Gln	95 Ser	Pro	

			7.00					105							
0.7	ь.	0.7	100	•	_	_		105			07	•	110		_
Glu	Phe	G1u 115	Ser	Gln	Ser	Pro	Arg 120	lyr	Glu	Pro	Gin	Ser 125	Pro	Gly	Tyr
Glu	Pro 130	Arg	Ser	Pro	Gly	Tyr 135	Glu	Pro	Arg	Ser	Pro 140	Gly	Tyr	Glu	Ser
G1u 145		Ser	Arg	Tyr	G1ս 150		Gln	Asn	Thr	G1u 155		Lys	Thr	Gln	Ser 160
	Glu	Phe	Glu	Ala 165		Ser	Ser	Lys	Phe 170		Glu	Gly	Ala	G1u 175	
Leu	Leu	Asn	Pro 180		Glu	Lys	Ser	Pro 185		Asn	Пe	Ser	Val 190	Gly	Val
His	Pro	Leu 195		Ser	Phe	Thr	G1n 200		Phe	Gly	Glu	G1n 205		Thr	Gly
Asp	Leu 210		Ile	Gly	Pro	Pro 215		Glu	Met	Pro	Thr 220		Ala	Leu	Leu
Ser 225	Thr	Pro	Gln	Phe	G1u 230	Met	Leu	Gln	Asn	Pro 235	Leu	Gly	Leu	Thr	Gly 240
Ala	Leu	Arg	Gly	Pro 245	Gly	Arg	Arg	Gly	G1y 250	Arg	Ala	Arg	Gly	Gly 255	Gln
Gly	Pro	Arg	Pro 260	Asn	Ile	Cys	Gly	Ile 265	Cys	Gly	Lys	Ser	Phe 270	Gly	Arg
Gly	Ser	Thr 275	Leu	Ile	Gln	His	G1n 280	Arg	Ile	His	Thr	G1y 285	Glu	Lys	Pro
Tyr	Lys 290	Cys	Glu	Val	Cys	Ser 295	Lys	Ala	Phe	Ser	G1n 300	Ser	Ser	Asp	Leu
Ile 305	Lys	His	G1n	Arg	Thr 310	His	Thr	Gly	Glu	Arg 315	Pro	Tyr	Lys	Cys	Pro 320
Arg	Cys	Gly	Lys	A1a 325	Phe	Ala	Asp	Ser	Ser 330	Tyr	Leu	Leu	Arg	His 335	G1n
Arg	Thr	His	Ser 340	Gly	Gln	Lys	Pro	Tyr 345	Lys	Cys	Pro	His	Cys 350	Gly	Lys
Ala	Phe	Gly 355	Asp	Ser	Ser	Tyr	Leu 360	Leu	Arg	His	Gln	Arg 365	Thr	His	Ser
His	G1u 370	Arg	Pro	Tyr	Ser	Cys 375	Thr	Glu	Cys	Gly	Lys 380	Cys	Tyr	Ser	Gln
Asn 385		Ser	Leu	Arg	Ser 390	His	Gln	Arg	Val	His 395	Thr	Gly	Gln	Arg	Pro 400
Phe	Ser	Cys	G1y	Ile 405	Cys	Gly	Lys	Ser	Phe 410	Ser	Gln	Arg	Ser	Ala 415	Leu
He	Pro	His	A1a 420	Arg	Ser	His	Ala	Arg 425	Glu	Lys	Pro	Phe	Lys 430	Cys	Pro
Glu	Cys	Gly 435		Arg	Phe	Gly	G]n 440		Ser	Val	Leu	Ala 445		His	Ala
Δra	Thr		Leu	Dro	Glv	Δrα		Tyr	Ser	Cvs	Pro	Δsn	Cvc	Glv	Lve

	450)				455	· •				460)				
Thr 465	Ph∈	e Asr	n Arg	Ser	Ser 470		. Ler	ı Ile	e Gln	His 475	G1r		l Ser	His	5 Thr 480	
Gly	Glu	ı Arç	Pro	7yr 485		Cys	Ala	Val	Cys 490		' Lys	Gly	Phe	Cys 495	s Arg	
			500)				505	· •				510)	g Pro	
		515	•				520	ì				525		· Asp	Leu	
Ile	Arg 530		G1n	ı Arg	Thr	His 535		Ala	Gly	Arg	Arg 540					
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atc Ile	ctc Leu	atc Ile	cag Gln 20	acc Thr	aac Asn	cag Gln	ctt Leu	acc Thr 25	999 Gly	gag Glu	ccc Pro	gag Glu	ctc Leu 30	cac His	tac Tyr	96
ctg Leu	agg Arg	ctg Leu 35	ccc Pro	aag Lys	gac Asp	atc Ile	agc Ser 40	gat Asp	gac Asp	cac His	gtg Val	atc Ile 45	ctc Leu	atg Met	gac Asp	144
gc Cys	acc Thr 50	gtg Val	tcc Ser	acg Thr	ggc Gly	gcg Ala 55	gcg Ala	gcc Ala	atg Met	atg Met	gca Ala 60	gtg Val	cgc Arg	gtg Val	ctc Leu	192
tg .eu 65	gac Asp	cac His	gac Asp	gtg Val	cct Pro 70	gag Glu	gac Asp	aag Lys	atc Ile	ttt Phe 75	ttg Leu	ctg Leu	tcg Ser	ctg Leu	ctc Leu 80	240
itg let	gca Ala	gag Glu	atg Met	ggc Gly	gtg Val	cac His	tca Ser	gtg Val	gcc Ala	tat Tyr	gca Ala	ttt Phe	ccg Pro	cga Ara	gtg Val	288

85 90 95

aga atc atc acc acg gcg gtg gac aag cgg gtc aat gac ctt ttc cgc 336 Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100 105 atc atc cca ggc att ggg aac ttt ggc gac cgc tac ttt ggg aca gac 384 Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp 115 120 125 gcg gtc ccc gat ggc agt gac gag gag gaa gtg gcc tac acg ggt tag 432 Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly * 130 135

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<211> 143

<212> PRT

<213> Homo sapiens

<400> 24

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Leu Arg Leu Pro Lys Asp Ile Ser Asp Asp His Val Ile Leu Met Asp

35 40 45
Thr Val Ser Thr Gly Ala Ala Ala Met Met Ala Val Arg Val Leu

Cys Thr Val Ser Thr Gly Ala Ala Ala Met Met Ala Val Arg Val Leu 50 55 60

Leu Asp His Asp Val Pro Glu Asp Lys Ile Phe Leu Leu Ser Leu Leu 65 70 75 80

Met Ala Glu Met Gly Val His Ser Val Ala Tyr Ala Phe Pro Arg Val 85 90 95

Arg Ile Ile Thr Thr Ala Val Asp Lys Arg Val Asn Asp Leu Phe Arg 100 105 110

Ile Ile Pro Gly Ile Gly Asn Phe Gly Asp Arg Tyr Phe Gly Thr Asp

Ala Val Pro Asp Gly Ser Asp Glu Glu Glu Val Ala Tyr Thr Gly 130 135 140

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ctc Leu	acc Thr	acc Thr	acc Thr 20	ggc Gly	ctc Leu	ttc Phe	ttc Phe	gto Val 25	Phe	gac Asp	tgt Cys	ccc Pro	tac Tyr 30	Leu	gct Ala	96
			Thr					Ile	atc Ile				Leu		ttc Phe	144
									agc Ser							192
									gcc Ala							240
									cca Pro 90							288
									ctg Leu							336
									cac His							384
tgt Cys	gtg Val 130	gaa Glu	cgą Arg	ttt Phe	gac Asp	cat His 135	cac His	tgc Cys	ccc Pro	tgg Trp	gtg Val 140	ggc Gly	aac Asn	tgt Cys	gtg Val	432
									gcg Ala							480

145					150					155	;				160		
					He					Val					ttg Leu	5	28
									Thr					cca Pro		5	76
								Phe					Ser	att Ile		6	24
ggc Gly	ctc Leu 210	tca Ser	999 Gly	ttt Phe	cac His	acg Thr 215	tac Tyr	ctc Leu	gtc Val	gcc Ala	tcc Ser 220	aac Asn	ctg Leu	act Thr	act Thr	6	72
aat Asn 225	gaa Glu	gac Asp	atc Ile	aaa Lys	ggc Gly 230	tcg Ser	tgg Trp	tcc Ser	agc Ser	aag Lys 235	agg Arg	ggc Gly	ggt Gly	gag Glu	gcc Ala 240	7:	20
tct Ser	gtc Val	aac Asn	ccc Pro	tac Tyr 245	agc Ser	cat His	aaa Lys	agt Ser	att Ile 250	atc Ile	acc Thr	aac Asn	tgc Cys	tgt Cys 255	gct Ala	76	68
gtg Val	ctc Leu	tgt Cys	ggc Gly 260	ccc Pro	cta Leu	cct Pro	ccc Pro	agc Ser 265	cta Leu	att Ile	gac Asp	cgg Arg	agg Arg 270	gga Gly	ttt Phe	81	16
						Leu								gag Glu		86	54
41a	tgc Cys 290	aga Arg	gcc Ala	aag Lys	cct Pro	gat Asp 295	gcc Ala	agc Ser	atg Met	gta Val	gga Gly 300	ggc Gly	cac His	ccc Pro	tga *	91	12

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<211> 303

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<213> Homo sapiens

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<211> 795

<212> DNA

<213> Homo sapiens

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	<	:222>	· mis · (1) · n =	(795)											
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				Gly					Phe					Пe	acc Thr	96
			Leu					He						aat Asn	gga Gly	144
														gaa Glu		192
														gaa Glu		240
														aaa Lys 95		288
Leu	Lys	Thr	aaa Lys 100	Tyr	Glu	Gln	Lys	Lys	Asn	agt Ser	gta Val	cca Pro	tct Ser 110	ata Ile	ttg Leu	336
cgt Arg	agt Ser	aac Asn 115	aga Arg	ttt Phe	cgc Arg	aga Arg	gat Asp 120	gca Ala	aaa Lys	gcc Ala	ttg Leu	gaa Glu 125	gag Glu	gat Asp	gaa Glu	384
gaa Glu	atg Met	tgg Trp	ttt Phe	aat Asn	gaa Glu	gat Asp	gaa Glu	gaa Glu	gag G1u	gaa Glu	gga Gly	aaa Lys	gca Ala	gtt Val	gtg Val	432

	130					135					140						
	Pro					Lys									tat Tyr 160		480
gaa Glu	aag Lys	ttt Phe	atg Met	gag Glu 165	act Thr	aaa Lys	aaa Lys	gca Ala	aaa Lys 170	gaa Glu	agt Ser	gaa Glu	gac Asp	aag Lys 175	gaa Glu		528
												ttt Phe					576
												tct Ser 205					624
cag Gln	ata Ile 210	cca Pro	cca Pro	gca Ala	act Thr	tct Ser 215	aat Asn	gga Gly	tcc Ser	tct Ser	tcc Ser 220	aaa Lys	acc Thr	aca Thr	aac Asn		672
												gtt Val				• 10	720
												gnn Xaa					768
			cct Pro 260					taa *									795
	<2 <2	11> 11> 12> 13>	264	sap	iens												
	<2 <2	22>	VARI (1). Xaa	(2		ino	Acid										

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<211> 711

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<213> Homo sapiens

<220>

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												tcc Ser 45					144
											_	gaa Glu			-		192
												gta Val					240
												tca Ser					288
												gca Ala					336
												aat Asn 125				=	384
												aag Lys					432
				Glu								aac Asn					480
cag	ctg	gct	gga	ctg	aca	ttg	ttg	aca	aac	atg	act	gtt	acc	aat	gac		528

Gln	l Leu	ı Ala	ı G1y	Leu 165		Leu	Leu	Thr	Asn 170		. Thr	· Val	Thr	Asn 175	•	
				Leu					Thr		ctg Leu			Val		576
ctt Leu	act Thr	gga Gly 195	Asn	gga Gly	aac Asn	acg Thr	aag Lys 200	Val	caa G1n	gtt Val	ttg Leu	aaa Lys 205	Leu	ctt Leu	ttg Leu	624
aat Asn	ttg Leu 210	Ser	gaa Glu	aat Asn	cca Pro	gcc Ala 215	atg Met	aca Thr	gaa G1u	gga Gly	ctt Leu 220	Leu	cgt Arg	gcc Ala	caa G1n	672
	Asp										acg Thr					711
	<; <; <;		236 PRT Homo	o sap	oiens	5 .										
Met 1		400> Gly		Arg 5	Gly	Ala	Gly	Trp		Ala	Ala	Gly	Leu		Leu	
	Ala	Gly	Ala 20		Tyr	Cys	Пe	Tyr 25	10 Arg	Leu	Thr	Arg	G1y 30	15 Arg	Arg	
Arg	Gly	Asp 35	Arg	Glu	Leu	Gly	Ile 40		Ser	Ser	Lys	Ser 45		Glu	Asp	
Leu	Thr 50	Asp	Gly	Ser	Tyr	Asp 55	Asp	Val	Leu	Asn	Ala 60	Glu	Gln	Leu	Gln	
Lys 65	Leu	Leu	Tyr		Leu 70	Glu	Ser	Thr	G1u	Asp 75	Pro	Val	Пе	Ile	G1u 80	
Arg	Ala	Leu	Ile	Thr 85	Leu	Gly	Asn	Asn	A1a 90		Phe	Ser	Val	Asn 95		
Ala	Ile	Ile	Arg 100		Leu	Gly	G1y	Ile 105		Ile	Val	Ala	Asn 110		Ile	
Asn	His	Ser 115		G1n	Ser		Lys 120		Lys	Ala	Leu	Asn 125		Leu	Asn	
Asn	Leu	Ser	Va1	Asn	Val	Glu	Asn	Gln	Пе	Lys	He		Ile	Tyr	Ile	

Ser 145		Va1	Cys	Glu	Asp 150		Phe	: Ser	Gly	Pro 155	Leu	Asn	Ser	Ala	Val 160	
G1n	Leu	Ala	Gly	Leu 165		Leu	Leu	Thr	Asn 170	Met		Val	Thr	Asn 175	Asp	
			180					185		·			190		Leu	
		195					200				Leu	205				
	210					215					Leu 220		Arg	Ala	Gln	
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	<	212>	31 173 DNA Home		pien	S										
	<		CDS (1)	(1737)										
ata		400>		cac	000	aca	000	o+a	ot o	029	2+2	o.t.o.				
											ctg Leu					48
											tcg Ser					96
											cac					144
											cgg Arg 60					192
											acc Thr					240
cag	gag	tgg	ctg	gcg	gct	gtg	ggc	gat	gac	tat	gct	gct	gtg	gtc	tgg	288

Gln	Glu	Trp	Leu	A1 a 85		Val	Gly	' Asp	Asp 90		· Ala	ı Ala	Val	Val 95	Trp		
				Glu					Pro					Pro	aag Lys		336
			Lys					Phe					Lys		gaa Glu		384
gcc Ala	ctc Leu 130	acc Thr	ttt Phe	gcc Ala	agg Arg	aac Asn 135	tgg Trp	999 Gly	gcc Ala	gac Asp	tat Tyr 140	atc Ile	ctg Leu	ttt Phe	gca Ala		432
			aac Asn														480
			ctt Leu														528
tac Tyr	tcc Ser	aac Asn	ttc Phe 180	tgg Trp	tgt Cys	999 Gly	atc Ile	acc Thr 185	ccc Pro	cag Gln	ggc Gly	tac Tyr	tac Tyr 190	cgc Arg	cgc Arg		576
aca Thr	gcc Ala	gag Glu 195	tac Tyr	ttc Phe	ccc Pro	Thr	aag Lys 200	aac Asn	cgc Arg	cag Gln	cgc Arg	cgg Arg 205	ggc Gly	tgc Cys	ttc Phe		624
٩rg	gtc Val 210	ccc Pro	atg Met	gtc Val	cac His	tcc Ser 215	acc Thr	ttc Phe	ctt Leu	gca Ala	tcc Ser 220	ctg Leu	cgg Arg	gct Ala	gaa Glu		672
			cag Gln	Leu													720
ect Pro	ttc Phe	gac Asp	gac Asp	atc Ile 245	atc Ile	gtc Val	ttc Phe	Ala	tat Tyr 250	gcc Ala	tgc Cys	cag Gln	gct Ala	gct Ala 255	999 Gly	·	768
gtc	tcc	gtc	cac	gtg	tgc	aat	gag	cac	cgt	tat	ggg [*]	tac	atg	aat	gtg	8	316

Val	Ser	Val	His 260	Val	Cys	Asn	Glu	His 265	Arg	Tyr	Gly	Tyr	Met 270	Asn	Val	
			tcc Ser										aac			864
			tta Leu													912
			act Thr													960
	-		gtc Val		_	•	_	_			•	•		_	-	1008
			tcg Ser 340											_	-	1056
			ggc Gly													1104
			ctc Leu													1152
			gag Glu												_	1200
			gcc Ala													1248
			gag Glu 420				Arg									1296
gat	gtg	gag	gca	gag	aaa	ctg	tct	tgg	gac	ctg	atc	tac	ctc	gga	cgg	1344

Asp	Val	G1u 435	Ala	Glu	Lys	Leu	Ser 440		Asp	Leu	Пe	Tyr 445	Leu	Gly	Arg	
aag Lys	cag Gln 450	gtg Val	aac Asn	cct Pro	gag G1u	aag Lys 455	gag Glu	acg Thr	gcc Ala	gtg Val	gag Glu 460	ggg Gly	ctg Leu	ccg Pro	ggc Gly	1392
ctg Leu 465	gtg Val	gtg Val	gct Ala	ggg Gly	tac Tyr 470	tcc Ser	tac Tyr	tgg Trp	acg Thr	ctg Leu 475	gcc Ala	tat Tyr	gcc Ala	ctg Leu	cgt Arg 480	1440
						ctg Leu										1488
						ctg Leu										1536
						ttc Phe										1584
gcc Ala	cag Gln 530	ccc Pro	ctg Leu	ctc Leu	gct Ala	gcc Ala 535	cct Pro	acc Thr	cac His	tat Tyr	gcc Ala 540	999 Gly	gac Asp	gcc Ala	gag Glu	1632
tgg Trp 545	ctc Leu	agt Ser	gac Asp	Thr	gag Glu 550	aca Thr	tcc Ser	tct Ser	cca Pro	tgg Trp 555	gat Asp	gat Asp	gac Asp	agc Ser	ggc G1y 560	1680
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tgg Trp	acc Thr	tga *														1737

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<213> Homo sapiens

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Gly	Pro	Trp	Leu 20	Glu	Ala	Ala	Gly	Va1 25	Ala	Glu	Ser	Pro	Leu 30		Ala
Val	Val	Leu 35	Ala	Ile	Leu	Ala	Arg 40	Asn	Ala	Glu	His	Ser 45	Leu	Pro	His
Tyr	Leu 50	Gly	A1a	Leu	Glu	Arg 55	Leu	Asp	Tyr	Pro	Arg 60	Ala	Arg	Met	Ala
65					70					Asn 75					80
Gln	Glu	Trp	Leu	A1 a 85	Ala	Val	Gly	Asp	Asp 90	Tyr	Ala	Ala	Val	Va1 95	Trp
			100					105		Asp			110		
		115					120			Met		125	-		
	130					135				Asp	140				
145					150					Thr 155		_			160
				165					170	Leu				175	
			180					185		Gln			190	_	
		195					200			Gln		205			
	210					215				Ala	220				
225					230		-			His 235			Ť		240
				245					250	Ala				255	_
			260					265		Tyr			270		
		275					280			Glu		285			
	290					295				Pro	300				
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Glu	Val	Phe		Ile 325	Ser	Leu	Ala		Arg 330	Pro	Asp	Arg	Arg	G1u 335	

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Ala Val Asp Gly Trp Met Leu Asn Ser Ser Ala Ile Arg Asn Leu Gly
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Val Asp Leu Leu Pro Gly Tyr Gln Asp Pro Tyr Ser Gly Arg Thr Leu
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Thr Lys Gly Glu Val Gly Cys Phe Leu Ser His Tyr Ser Ile Trp Glu
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Glu Val Val Ala Arg Gly Leu Ala Arg Val Leu Val Phe Glu Asp Asp
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Val Arg Phe Glu Ser Asn Phe Arg Gly Arg Leu Glu Arg Leu Met Glu
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Asp Val Glu Ala Glu Lys Leu Ser Trp Asp Leu Ile Tyr Leu Gly Arg
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                                               445
Lys Gln Val Asn Pro Glu Lys Glu Thr Ala Val Glu Gly Leu Pro Gly
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Leu Val Val Ala Gly Tyr Ser Tyr Trp Thr Leu Ala Tyr Ala Leu Arg
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                                       475
Leu Ala Gly Ala Arg Lys Leu Leu Ala Ser Gln Pro Leu Arg Arg Met
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Leu Pro Val Asp Glu Phe Leu Pro Ile Met Phe Asp Gln His Pro Asn
           500
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Ala Gln Pro Leu Leu Ala Ala Pro Thr His Tyr Ala Gly Asp Ala Glu
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Trp Leu Ser Asp Thr Glu Thr Ser Ser Pro Trp Asp Asp Ser Gly
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														ttg Leu		336
														aga Arg		384
														agc Ser		432
														cca Pro		480
														atg Met 175		528
atg	tat	gtg	ctt	gga	atg	gca	gaa	gaa	ttt	aaa	ggt	gaa	att	gca	gtc	576

Met	Tyr	Val	Leu 180		Met	Ala	Glu	Glu 185		Lys	Gly	Glu	Ile 190		Val	
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						gaa Glu 215										672
						att Ile										720
						aat Asn									aat. Asn	768
						aaa Lys										816
						gaa Glu										864
						aaa Lys 295				_	_	-				912
						gaa Glu										960
			Asp			aaa Lys										1008
		Gly				ggc Gly	Thr									1056
ggt	999	aat	gtc	gga	tat	gga	gag	cct	tct	gat	cag	gca	gat	gtg	gtg	1104

Gly Gly Asn Val Gly Tyr Gly Glu Pro Ser Asp Gln Ala Asp Val Val 355 360 365

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215

230

Ala Asp Ala Ala Tyr Ser Ile Phe Gln Lys Pro Lys Ser Phe Thr Gly

Asn	Phe	Val	He	Asp 245	Glu	Asn	Пe	Leu	Lys 250	Glu	Glu	Gly	Ile	G1u 255	Asn		
Phe	Asp	Val	Tyr 260	Ala	Ile	Lys	Pro	Gly 265	His	Pro	Leu	Gln	Pro 270	Asp	Phe		
Phe	Leu	Asp 275	Glu	Tyr	Pro	Glu	A1a 280	Val	Ser	Lys	Lys	Val 285	Glu	Ser	Thr		
Gly	Ala 290		Pro	Glu	Phe	Lys 295		Glu	Lys	Leu	G1n 300		Gln	Pro	Lys		
Pro 305		Ser	Gly	Ala	Val 310		Glu	Thr	Phe	Arg 315		Val	Lys	Asp	Ser 320	a .	
	Ser	Asp	Asp	Va1 325	Val	Lys	Ala	Thr	Gln 330		Ile	Tyr	Leu	Phe 335			
Leu	Ser	Gly	G1u 340	Asp	Gly	Gly	Thr	Trp 345	Phe	Leu	Asp	Leu	Lys 350		Lys		
Gly	Gly	Asn 355	Val	Gly	Tyr	Gly	G1u 360	Pro	Ser	Asp	Gln	Ala 365	Asp	Val	Val		
Met	Ser 370	Met	Thr	Thr	Asp	Asp 375	Phe	Val	Lys	Met	Phe 380	Ser	Gly	Asn			
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	Leu								Val		cag Gln	192
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				-	_	 -		ttc Phe				336
								ccc Pro				384
								ctg Leu 140				432
								acc Thr				480
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				Arg				ggc Gly				624
Thr			Leu					gtg Val 220				672

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										gag Glu 315						960
										ctc Leu						1008
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						Met				aca Thr						1104
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Arg	Asn	Ser 35	20 Thr	Val	Ser	Arg	Leu 40	25 Ile	Phe	Thr	Phe	Phe 45	30 Leu	Phe	Leu	
Gly	Val 50		Val	Ser	Пе	Ile 55		Leu	Ser	Pro	Gly 60		Glu	Ser	Gln	
Leu 65		Lys	Leu	Pro	Trp 70		Cys	Glu	G1u	Gly 75		Gly	Ile	Pro	Thr 80	
	Leu	Gln	Gly	His 85		Asp	Cys	Gly	Ser 90		Leu	Gly	Tyr	Arg 95		
Val	Tyr	Arg	Met 100		Phe	Ala	Thr	Ala 105		Phe	Phe	Phe	Phe 110		Thr	
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Tyr	Phe	Gly	Val	Val 165	Gly		Phe	Leu	Phe 170	Пe		Ile	Gln	Leu 175	
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Αla	Glu	Glu 195		Asp	Ser	Arg	A1a 200	Trp	Tyr	Ala	Gly	Leu 205	Phe	Phe	Phe
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				Thr 245					250					255	
			260	Asp				265					270		
		275		Tyr			280			·		285			
	290			Lys		295					300			-	
305				Ala	310					315			·		320
				Va1 325					330					335	
Пe	Ser	Leu	Arg 340	Ser	Ser	Asp	His	Arg 345	G1n	Val	Asn	Ser	Leu 350	Met	Gln
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	370			Cys		375				-	380			·	_
385				Tyr	390					395					400
				Met 405					410					415	
Arg	Lys	Met	I1e 420	Ser	Thr	Trp	Thr	A1 a 425	Val	Trp	Val	Lys	Ile 430	Cys	Ala
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						agt Ser										336
						gat Asp										384
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				cag Gln						672
Asp				caa Gln			-			720
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Ile	Leu	Val	Asn 100	Asn	Ala	Ser	` Ala	lle 105	Ser	Leu	ı Thr	Asn	Thr 110	Leu	As
Thr	Pro	Thr 115	Lys		Leu	Asp	Leu 120	Met		: Asn	ı Val	Asn 125	Thr		Gly
Thr	Tyr 130		ı Ala	Ser	Lys	Ala 135		Ile	Pro	Tyr	Leu 140		Lys	Ser	Lys
Val 145		His	Ile	Leu	Asn 150		Ser	Pro	Pro	Leu 155		Leu	Asn	Pro	Va ⁻ 160
Trp	Phe	Lys	Gln	His 165		Ala	Tyr	Thr	Ile 170		Lys	Tyr	Gly	Met 175	
			Leu 180					185					190		
		195					200					205		·	
	210		Pro			215					220		•		
225			Ala		230					235					240
			Пe	245					250			_		255	
			Tyr 260					265					270		
		275	Glu				280					285			
	290		Pro			295					300				-
305			Gly		310					315					320
			Asp	325					330					335	
			G1u 340					345					350		
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Met	Ser 370	Met	Thr	Thr	Asp	Asp 375	Phe	Va1	Lys	Met	Phe 380	Ser	Gly	Lys	Leu
Lys 385	Pro	Thr	Met	Ala	Phe 390	Met	Ser	Gly	Lys	Leu 395	Lys	Пe	Lys	Gly	Asn 400
Met	Ala	Leu	Ala	He	Lvs	Leu	Glu	Lvc	Leu		Asn	Gln	Mot	Δcn	

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			ctg Leu													240
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			aaa Lys 100													336
			gat Asp													384

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gca Ala 145	gca Ala	gag Glu	aaa Lys	gaa Glu	tgc Cys 150	aga Arg	gat Asp	cgt Arg	gaa Glu	gag Glu 155	agg Arg	aat Asn	gag Glu	aaa Lys	aaa Lys 160	4	80
gcc Ala	caa Gln	att Ile	cag G1n	gaa Glu 165	atg Met	aaa Lys	aag Lys	aga Arg	gaa Glu 170	aaa Lys	gaa Glu	gaa Glu	atg Met	aag Lys 175	aag Lys	5	28
											tca Ser					5	76
gaa Glu	aat Asn	atg Met 195	tct Ser	tca Ser	aat Asn	cag Gln	gat Asp 200	ggc Gly	aat Asn	gat Asp	tca Ser	gat Asp 205	gaa Glu	ttc Phe	atg Met		24
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 Tyr
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 Ser
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 Val
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 Ala
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 Thr

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 1le
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 Met
 Gly
 Lys
 Asp
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 Tyr
 Glu
 Asn
 Glu
 Asp
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 Val
 Asp
 Lys
 Leu
 Ser
 Ala

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Lys	Arg	Glu	Met 180			Leu	Arg	Ser 185		Ser	Ser	Leu	Met 190	Lys		
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Gly Val Arg Asp Tyr Ala Ala Tyr Asn Val Leu Asp Asp Pro Glu Leu 85 90 95 cga caa ggc att aaa gac tat tcc aac tgg ccc acc atc ccg caa gtc Arg Gln Gly Ile Lys Asp Tyr Ser Asn Trp Pro Thr Ile Pro Gln Val 100 105 110 tac ctc aat ggc gag ttt gta ggg ggc tgt gac att ctt ctg cag atc Tyr Leu Asn Gly Glu Phe Val Gly Gly Cys Asp Ile Leu Leu Gln Met 115 120 125 cac cag aat ggg gac ttg gaa aaa aag ctg ggg atc cac	5
Arg Gln Gly Ile Lys Asp Tyr Ser Asn Trp Pro Thr Ile Pro Gln Value 100 105 110 110 105 110 110 105 110 110	
Tyr Leu Asn Gly Glu Phe Val Gly Gly Cys Asp Ile Leu Leu Gln Met 115 120 125 cac cag aat ggg gac ttg gtg gaa gaa ctg aaa aag ctg ggg atc cac	336 I
His Gln Asn Gly Asp Leu Val Glu Glu Leu Lys Lys Leu Gly Ile His 130 135 140	
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His	Gln 130	Asn	G1y	Asp	Leu	Val 135	Glu	Glu	Leu	Lys	Lys 140			Ile	His	
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								tac Tyr 25								. 96
								cgc Arg								144
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cct Pro 65	cag Gln	acg Thr	gga Gly	ggt Gly	acc Thr 70	tgg Trp	gag Glu	tca Ser	cag G1n	tgg Trp 75	tcc Ser	aag Lys	acc Thr	tcg Ser	cag Gln 80	240

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Thr	aat Asn 210	gac Asp	cac His	cag Gln	cac His	atg Met 215	ctt Leu	cac His	agt Ser	tac Tyr	att Ile 220	aca Thr	gac Asp	ctg Leu	ttc Phe	672
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gca aag gag att ctt ctt cga gta ctt acg cta ttt cag aat ata a Ala Lys Glu Ile Leu Leu Arg Val Leu Thr Leu Phe Gln Asn Ile L 275 280 285	_
aac tgc ctc aaa ata gaa ggc cat tta gct gtg cag cct act ttc a Asn Cys Leu Lys Ile Glu Gly His Leu Ala Val Gln Pro Thr Phe T 290 295 300	
gaa ggt tca ttg ttt ttc ctg tta cat gga gaa gaa tgt gcc cag a Glu Gly Ser Leu Phe Phe Leu Leu His Gly Glu Glu Cys Ala Gln L 305 310 315 3	
ata aga gct tta gtt gat cac cat gat gca gag gtg aag gaa aag g Ile Arg Ala Leu Val Asp His His Asp Ala Glu Val Lys Glu Lys V 325 330 335	
gta aca ata ata ccc aaa atc tga Val Thr Ile Ile Pro Lys Ile * 340 ·	1032
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Gly Ala Gly Ala Cys Tyr Cys Ile Tyr Arg Leu Thr Arg Gly Arg Ai 20 25 30	ırg
Arg Gly Asp Arg Glu Leu Gly Ile Arg Ser Ser Lys Ser Ala Gly A' 35 40 45	.Ta
Leu Glu Glu Gly Thr Ser Glu Gly Gln Leu Cys Gly Arg Ser Ala Ai 50 55 60	rg
Pro Gln Thr Gly Gly Thr Trp Glu Ser Gln Trp Ser Lys Thr Ser G 65 70 75 80	
Pro Glu Asp Leu Thr Asp Gly Ser Tyr Asp Asp Val Leu Asn Ala G 85 90 95	

G1n	Leu	G1n	Lys 100		Leu	Tyr	Leu	Leu 105		Ser	Thr	Glu	Asp 110	Pro	Val
		115					120					125			
	130		Ala			135					140				
145			Asn		150					155					160
			Asn	165					170				-	175	•
			Ser 180					185					190		
		195					200					205			
	210		His			215					220		·		
225			Leu		230					235					240
			Asn	245				,	250					255	
			Val 260					265				•	270		
		275	Ile				280					285			•
	290		Lys			295					300				
305			Leu		310					315					320
			Leu	325			піѕ	ASP	330	GIU	vai	Lys		Lys 335	vai
vui	1111	116	Ile 340	rio	Lys	116									
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											ttg Leu					144
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											gtg Val					240
											gtc Val					288
						-		-			ttc Phe					336
											cag Gln					384
											gtg Val 140					432
											gaa Glu					480
gaa	tat	aag	ссс	ctt	tcg	ggc	att	cgg	tac	atg	tgg	tcg	tac	cat	tta	528

Glu	Tyr	Lys	Pro	Leu 165		Gly	Ile	Arg	Tyr 170		Trp	Ser	· Tyr	His 175	Leu	
				Trp					He					Gln	atg Met	576
			Gly										Ser		aat Asn	624
gat Asp	cct Pro 210	cct Pro	gat Asp	cat His	ccc Pro	atc Ile 215	ctt Leu	tcg Ser	tct Ser	ctc Leu	tcc Ser 220	att Ile	ctc Leu	ttc Phe	ttc Phe	672
tac Tyr 225	cat His	caa Gln	gga Gly	acc Thr	att Ile 230	gtg Val	aaa Lys	ggg Gly	tca Ser	ttt Phe 235	tta Leu	atc Ile	tct Ser	gtg Val	gtg Val 240	720
				atc Ile 245												768
cag G1n	cat His	ggt Gly	gca Ala 260	ttg Leu	tcc Ser	agg Arg	tac Tyr	ctg Leu 265	ttc Phe	cga Arg	tgc Cys	tgc Cys	tac Tyr 270	tgc Cys	tgt Cys	816
			Leu	gac Asp		Tyr										864
act Thr	aca Thr 290	act Thr	gct Ala	att Ile	aat Asn	999 Gly 295	aca Thr	gat Asp	ttc Phe	tgt Cys	aca Thr 300	tca Ser	gca Ala	aaa Lys	gat Asp	912
gca 41a 305	ttc Phe	aaa Lys	atc Ile	ttg Leu	tcc Ser 310	aag Lys	aac Asn	tca Ser	Ser	cac His 315	ttt Phe	aca Thr	tct Ser	att Ile	aac Asn 320	960
tgc Cys	ttt Phe	gga Gly	Asp	ttc Phe 325	ata Ile	att Ile	ttt Phe	Leu	gga G1y 330	aag Lys	gtg Val	tta Leu	gtg Val	gtg Val 335	tgt Cys	1008
tc	act	gtt	ttt	gga	gga	ctc	atg (gct	ttt	aac	tac	aat	caa	аса	ttc	1056

Phe Thr Val Phe Gly Gly Leu Met Ala Phe Asn Tyr Asn Arg Ala Phe 340 345 350	
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gta gcc cat agt ttt tta tct gtg ttt gaa act gtg ctg gat gca ctt Val Ala His Ser Phe Leu Ser Val Phe Glu Thr Val Leu Asp Ala Leu 370 375 380	1152
ttc ctg tgt ttt gct gtt gat ctg gaa aca aat gat gga tcg tca gaa Phe Leu Cys Phe Ala Val Asp Leu Glu Thr Asn Asp Gly Ser Ser Glu 385 '390 395 400	1200
aag ccc tac ttt atg gat caa gaa ttt ctg agt ttc gta aaa agg agc Lys Pro Tyr Phe Met Asp Gln Glu Phe Leu Ser Phe Val Lys Arg Ser 405 410 415	1248
aac aaa tta aac aat gca agg gca cag cag gac aag cac tca tta agg Asn Lys Leu Asn Asn Ala Arg Ala Gln Gln Asp Lys His Ser Leu Arg 420 425 430	1296
aat gag gag gga aca gaa ctc cag gcc att gtg aga tag Asn Glu Glu Gly Thr Glu Leu Gln Ala Ile Val Arg * 435 440	1335
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Val His Ile Phe Ile Ser Leu Val Ile Leu Gly Leu Leu Phe Val Cys	

		35					40					45			
Gly	Va1 50	Leu	ı Trp	Trp	Leu	ı Tyr 55	Tyr	- Asp) Tyr	Thr	Asr 60	Asp	Leu	ı Ser	· Ile
G1u 65	Leu	ı Asp	Thr	Glu	Arg 70	g Glu	ı Asr	n Met	Lys	Cys 75	Val	Leu	G1y	/ Phe	A1a 80
Ile	Val	Ser	Thr	Gly 85	Ile	. Thr	· Alá	a Val	Leu 90	ı Let	val	Leu	Πe	Ph∈ 95	· Val
			100					105	·)				110)	Asn
		115					120)				125			Thr
	130					135					140				Leu
145					150					155					160
				165					170		Trp			175	
			180					185			Ala		190		
		195					200				Asn	205		1	
	210					215					Ser 220				
225					230					235	Leu				240
				245					250		Asn		•	255	
			260					265			Cys		270		-
		275					280				Asn	285			-
	290					295					Thr 300				
305					310					315	Phe				320
				325					330		Val			335	
			340					345			Tyr		350		
		355					360					365			
	370					375					Va1 380				
Phe	Leu	Cys	Phe	Ala	Val	Asp	Leu	Glu	Thr	Asn	Asp	Gly	Ser	Ser	G1u

385 Lys		o Tyr	- Phe	e Met	390 Asp		ı Glu	ı Phe	. Leu	395 Ser		· Val	Lys	: Arg	400 Ser	
Asr	ı Lys	: Lei				ı Arg	Ala) Lys	His			ı Arg	
Asr	ı Glu	435	420 u Gly S		`G]∟	Leu	Gln 440			Val	Arg	I	430			
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gga Gly	gtg Val	tac Tyr	aag Lys 20	tcc Ser	gcg Ala	gag Glu	cag Gln	ggg Gly 25	gag Glu	gtg Val	gaa Glu	aac Asn	gga Gly 30	cga Arg	tgt Cys	96
att Ile	act Thr	aag Lys 35	ctg Leu	gaa Glu	aac Asn	atg Met	999 Gly 40	ttt Phe	cga Arg	gtg Val	gga Gly	caa G1n 45	gga Gly	ttg Leu	ata Ile	144
gaa Glu	agg Arg 50	ttt Phe	aca Thr	aaa Lys	gat Asp	act Thr 55	gca Ala	agg Arg	ttc Phe	aag Lys	gat Asp 60	gag Glu	tta Leu	gat Asp	atc Ile	192
			att Ile													240
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			cgc Arg													336

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cta Leu	cct Pro	gat Asp 35	Glu	ttt Phe	ata Ile	gaa Glu	tgt Cys 40	gaa Glu	gac Asp	cca Pro	gtg Val	gat Asp 45	His	gtt Val	gga Gly		144
aat Asn	gca Ala 50	act Thr	gca Ala	tcc Ser	cag Gln	gaa Glu 55	ctt Leu	ggt Gly	tat Tyr	ggt Gly	tgt Cys 60	ctc Leu	aag Lys	ttc Phe	ggc Gly		192
ggt Gly 65	cag Gln	gcc Ala	tac Tyr	agc Ser	gac Asp 70	gtg Val	gaa Glu	cac His	act Thr	tca Ser 75	gtc Val	cag Gln	tgc Cys	cat His	gcc Ala 80		240
									agg Arg 90								288
									tac Tyr								336
									gtg Val							;	384
cac His	act Thr 130	ggc Gly	act Thr	gca Ala	gta Val	999 Gly 135	aag Lys	ctg Leu	ttg Leu	acg Thr	ctt Leu 140	gga Gly	gga Gly	ctt Leu	ggg Gly	4	432
att Ile 145	tgg Trp	tgg Trp	ttt Phe	gtt Val	gac Asp 150	ctt Leu	att Ile	ttg Leu	cta Leu	att Ile 155	act Thr	gga Gly	999 Gly	ctg Leu	atg Met 160	2	180
									gtt Val 170		taa *					Ę	516

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<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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Lys Phe Lys Leu Phe Thr Leu Val Ser Ala Cys Ile Pro Val Phe Arg
20 25 30

ctg Leu	gct Ala	aga Arg 35	Arg	cgg Arg	aag Lys	aag Lys	ato Ile 40	Leu	ttt Phe	tac Tyr	tgt Cys	cac His	Phe	cca Pro	gat Asp	144
		Leu					Ser					ı Leu			gcc Ala	192
cca Pro 65	He	gac Asp	tgg Trp	ata Ile	gag Glu 70	Glu	tac Tyr	acc Thr	aca Thr	ggc Gly 75	Met	gca : Ala	gac Asp	tgc Cys	atc Ile 80	240
						aca Thr										288
						cct Pro										336
acc Thr	agc Ser	ttt Phe 115	gac Asp	tca Ser	gtt Val	gtt Val	cct Pro 120	gaa Glu	aag Lys	ctg Leu	gat Asp	gac Asp 125	cta Leu	gtc Val	ccc Pro	384
aag Lys	999 Gly 130	aaa Lys	aaa Lys	ttc Phe	ctg Leu	ctg Leu 135	ctc Leu	tcc Ser	atc Ile	aac Asn	aga Arg 140	tac Tyr	gaa Glu	agg Arg	aag Lys	432
						ctg Leu										480
						gag Glu										528
tat Tyr	gac Asp	G1u	aga Arg 180	gtc Val	ctg Leu	gag Glu	aat Asn	gtg Val 185	gaa Glu	cat His	tat Tyr	cag G1n	gaa Glu 190	ttg Leu	aag Lys	576
aaa .ys	Met	gtc Val 195	caa Gln	cag Gln	tcc Ser	gac Asp	ctt Leu 200	ggc Gly	cag G1n	tat Tyr	gtg Val	acc Thr 205	ttc Phe	ttg Leu	agg Arg	624

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tct Ser	ttc Phe 210	Ser	gac Asp	aaa Lys	cag Gln	aaa Lys 215	atc Ile	tcc Ser	ctc Leu	ctc Leu	cac His 220	Ser	tgc Cys	acg Thr	tgt Cys		672
gtg Val 225	Leu	tac Tyr	aca Thr	cca Pro	agc Ser 230	aat Asn	gag Glu	cac His	ttt Phe	ggc Gly 235	att Ile	gtc Val	cct Pro	ctg Leu	gaa G1u 240		720
gcc Ala	atg Met	tac Tyr	atg Met	cag Gln 245	tgc Cys	cca Pro	gtc Val	att Ile	gct Ala 250	gtt Val	aat Asn	tcg Ser	ggt Gly	gga Gly 255	ccc Pro		768
ttg Leu	gag Glu	tcc Ser	att Ile 260	gac Asp	cac His	agt Ser	gtc Val	aca Thr 265	ggg Gly	ttt Phe	ctg Leu	tgt Cys	gag Glu 270	cct Pro	gac Asp		816
ccg Pro	Val	cac His 275	ttc Phe	tca Ser	gaa Glu	Ala	ata Ile 280	gaa Glu	aag Lys	ttc Phe	atc Ile	cag Gln 285	aaa Lys	agt Ser	cat His		864
ccg Pro	tga *											ï					870

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 Adologo 52

 Met Pro Leu Leu Lys Leu Val His Gly Ser Pro Leu Val Phe Gly Glu 1

 Lys Phe Lys Leu Phe Thr Leu Val Ser Ala Cys Ile Pro Val Phe Arg 20

 Leu Ala Arg Arg Arg Arg Lys Lys Ile Leu Phe Tyr Cys His Phe Pro Asp 35

 Leu Leu Leu Lu Thr Lys Arg Asp Ser Phe Lu Lys Arg Leu Tyr Arg Ala 50

 Pro Ile Asp Trp Ile Glu Glu Tyr Thr Thr Gly Met Ala Asp Cys Ile 65

 Leu Val Asn Ser Gln Phe Thr Ala Ala Val Phe Lys Glu Thr Phe Lys 85

 Ser Leu Ser His Ile Asp Pro Asp Val Leu Tyr Pro Ser Leu Asn Val

5

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100
                               105
 Thr Ser Phe Asp Ser Val Val Pro Glu Lys Leu Asp Asp Leu Val Pro
                           120
                                               125
 Lys Gly Lys Lys Phe Leu Leu Ser Ile Asn Arg Tyr Glu Arg Lys
                        135
 Lys Asn Leu Thr Leu Ala Leu Glu Ala Leu Val Gln Leu Arg Gly Arg
                    150
                                       155
 Leu Thr Ser Gln Asp Trp Glu Arg Val His Leu Ile Val Ala Gly Gly
                165
                                   170
 Tyr Asp Glu Arg Val Leu Glu Asn Val Glu His Tyr Gln Glu Leu Lys
                               185
 Lys Met Val Gln Gln Ser Asp Leu Gly Gln Tyr Val Thr Phe Leu Arg
                           200
                                              205.
 Ser Phe Ser Asp Lys Gln Lys Ile Ser Leu Leu His Ser Cys Thr Cys
                       215
 Val Leu Tyr Thr Pro Ser Asn Glu His Phe Gly Ile Val Pro Leu Glu
 225
                   230
                                      235
Ala Met Tyr Met Gln Cys Pro Val Ile Ala Val Asn Ser Gly Gly Pro
                245
                                   250
Leu Glu Ser Ile Asp His Ser Val Thr Gly Phe Leu Cys Glu Pro Asp
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Pro Val His Phe Ser Glu Ala Ile Glu Lys Phe Ile Gln Lys Ser His
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tct Ser	cgg Arg	gac Asp 35	Arg	aat Asn	tac Tyr	cag Gln	ggc G1y 40	' Ile	gtg Val	caa Glr	ı tat ı Tyr	gca Ala 45	ı Val	tcc Ser	ctt Leu	144
gtg Val	gat Asp 50	Ala	ctc Leu	ctc Leu	ttc Phe	atc Ile 55	cat His	tac Tyr	ctg Leu	gcc Ala	ato Ile 60	Val	ctg Leu	ctg Leu	gag Glu	192
ctc Leu 65	Arg	cag Gln	ctg Leu	cag G1n	ccc Pro 70	atg Met	ttc Phe	acg Thr	ctg Leu	cag Gln 75	Val	gtc Val	cgc Arg	tcc Ser	acc Thr 80	240
gat Asp	ggc Gly	gag Glu	tcc Ser	cgc Arg 85	Phe	tac Tyr	agc Ser	ctg Leu	gga Gly 90	cac His	ctg Leu	agt Ser	atc Ile	cag G1n 95	cga Arg	288
														atc Ile		336
														cat His		384
														gcc Ala		432
ggc Gly 145	cag Gln	tcc Ser	cgg Arg	gcc Ala	atg Met 150	att Ile	gct Ala	gca Ala	gct Ala	gct Ala 155	cgg Arg	cgc Arg	agg Arg	gac Asp	tca Ser 160	480
			Glu					Glu						cga Arg 175		528
		Arg					Val							ttc Phe		576

cac His	att Ile	cag Gln 195	ı Arg	cto Leu	cag Gln	gct Ala	gag Glu 200	Glu	cag Gln	cag Gln	aaa Lys	gcc Ala 205	Pro	999 Gly	gag Glu	624
gtg Val	atg Met 210	Asp	cct Pro	agg Arg	gag Glu	gcc Ala 215	gcc Ala	cag Gln	gcn Xaa	att Ile	ttc Phe 220	ccc Pro	tcc Ser	atg Met	gcc Ala	672
agg Arg 225	gct Ala	ctc Leu	cag Gln	aag Lys	tac Tyr 230	ctg Leu	cgc Arg	atc Ile	acc Thr	cgg Arg 235	cag Gln	cag G1n	aac Asn	tac Tyr	cac His 240	720
agc Ser	atg Met	gag Glu	agc Ser	atc Ile 245	ctg Leu	cag Gln	cac His	ctg Leu	gcc Ala 250	ttc Phe	tgc Cys	atc Ile	acc Thr	aac Asn 255	ggc Gly	768
atg Met	acc Thr	ccc Pro	aag Lys 260	gcc Ala	ttc Phe	cta Leu	gaa Glu	cgg Arg 265	tac Tyr	ctc Leu	agt Ser	gcg Ala	ggc Gly 270	ccc Pro	acc Thr	816
ctg Leu	caa Gln	tat Tyr 275	gac Asp	aag Lys	gac Asp	cgc Arg	tgg Trp 280	ctc Leu	tct Ser	aca Thr	cag G1n	tgg Trp 285	agg Arg	ctt Leu	gtc Val	864
agt Ser	gat Asp 290	gag G1u	gct Ala	gtg Val	act Thr	aat Asn 295	gga Gly	tta Leu	cgg Arg	gat Asp	gga Gly 300	att Ile	gtg Val	ttc Phe	gtc Val	912
ctt Leu 305	aag Lys	tgc Cys	ttg Leu	gac Asp	ttc Phe 310	agc Ser	ctc Leu	gta Val	Val	aat Asn 315	gtg Val	aag Lys	aaa Lys	att Ile	cca Pro 320	960
ttc Phe	atc Ile	ata Ile	ctc Leu	tct Ser 325	gaa Glu	gag Glu	ttc Phe	Пe	gac Asp 330	ccc Pro	aaa Lys	tct Ser	His	aaa Lys 335	ttt Phe	1008
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<211> 346

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

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<223> Xaa = Any Amino Acid

<400> 54

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Ser	Asp 290	Glu	Ala	val	Thr	Asn 295	Gly	Leu	Arg	Asp	Gly 300		Va1	Phe	Val	
305				Asp	310					315			·		320	
Phe	Ile	Ile	Leu	Ser 325	Glu	Glu	Phe	Ile	Asp 330		Lys	Ser	His	Lys 335	Phe	
Val	Leu	Arg	Leu 340	Gln	Ser	Glu	Thr	Ser 345	Val							
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gaa Glu	cgc Arg	agg Arg 35	aag Lys	aag Lys	gaa Glu	gcc Ala	aac Asn 40	aag Lys	gcg Ala	aca Thr	aga Arg	gcc Ala 45	aac Asn	cac His	aac Asn	144
:gg \rg	aga Arg 50	acc Thr	atg Met	gcc Ala	gac Asp	cgc Arg 55	aag Lys	agg Arg	agc Ser	aaa Lys	ggc Gly 60	atg Met	atc Ile	cca Pro	tcc Ser	192
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<213> Homo sapiens

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Val	I Ala	a Gly	/ Ser 20	r Pro) Arg	g Gly	/ His	Gly 25		ı Ser	r Arg	g Gl∟	Thr	Th	r Gln	
G1L	ı Arg	g Arg 35	j Lys	S Lys	G Tu	ı Ala	Asr 40	ı Lys	6 A 1 a	a Thr	n Arg	Ala 45		Hi:	s Asn	
Arg	9 Arg 50	g Thr	Met	Alá	a Asp	Arg 55	, Lys	: Arg	g Ser	Lys	60 60		: Ile	e Pro	Ser	
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aga Arg	cct Pro	tca Ser	ggt Gly 20	ggt Gly	gct Ala	gct Ala	ggg Gly	gaa Glu 25	cgg Arg	gag Glu	ctg Leu	gat Asp	gag Glu 30	gtt Val	gat Asp	96
atg Met	tca Ser	gat Asp 35	ctc Leu	tct Ser	cca Pro	gaa G1u	gag Glu 40	caa Gln	tgg Trp	agg Arg	gtc Val	gag Glu 45	cac His	gca Ala	cgc Arg	144
atg Met	cat His 50	gcc Ala	aag Lys	cac His	cgt Arg	ggc Gly 55	cat His	gaa Glu	gct Ala	atg Met	cat His 60	gct Ala	gaa Glu	atg Met	gtc Val	192
ctc Leu 65	atc Ile	ctc Leu	atc Ile	gca Ala	acc Thr 70	ttg Leu	gtg Val	gtg Val	gcc Ala	cag Gln 75	ctg Leu	ctc Leu	ctg Leu	gtg Val	cag Gln .80	240
tgg Trp	aag Lys	cag G1n	agg Arg	cac His 85	cca Pro	cgc Arg	tcc Ser	tac Tyr	aat Asn 90	atg Met	gtg Val	acc Thr	ctc Leu	ttt Phe 95	cag G1n	288

atg Met	tgg Trp	gtt Val	gtt Val 100	Pro	ctc Leu	tat Tyr	ttc Phe	aca Thr 105	` Val	aag Lys	ctg Leu	cac His	tgg Trp 110	Trp	agg Arg	336
			Ile					Ser					Phe		acc Thr	384
ttc Phe	cga Arg 130	gcc Ala	acc Thr	cga Arg	aaa Lys	cct Pro 135	cta Leu	gta Val	cag G1n	aca Thr	acc Thr 140	Pro	agg Arg	ttg Leu	gtt Val	432
tat Tyr 145	aag Lys	tgg Trp	ttc Phe	ctg Leu	cta Leu 150	atc Ile	tat Tyr	aaa Lys	atc Ile	agc Ser 155	tat Tyr	gcc Ala	act Thr	ggc Gly	att Ile 160	480
gtt Val	ggc Gly	tac Tyr	atg Met	gct Ala 165	gtc Val	atg Met	ttt Phe	acc Thr	ctc Leu 170	ttt Phe	ggt Gly	ctt Leu	aac Asn	tta Leu 175	tta Leu	528
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tgt Cys	gca Ala 210	gac Asp	tac Tyr	atg Met	gca Ala	tct Ser 215	acc Thr	ata Ile	999 Gly	ttc Phe	tac Tyr 220	agc Ser	gag Glu	tcg Ser	ggc Gly	672
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igg irg	ctg Leu	Ser	tgc Cys 260	aat Asn	cat His	gtc Val	Phe	cac His 265	gag Glu	ttc Phe	tgc Cys	Ile	cgt Arg 270	ggc Gly	tgg Trp	816

	atc Ile															864
	ctc Leu 290															912
	999 Gly															960
gtc Val	atc Ile	att Ile	ggt Gly	gta Val 325	gtc Val	caa Gln	ggc Gly	atc Ile	aac Asn 330	tac Tyr	atc Ile	ctg Leu	ggc Gly	ctg Leu 335	gaa Glu	1008
tag *																1011

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 Arg

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 Ala
 Ala
 Gly
 Glu
 Arg
 Glu
 Leu
 Asp
 Glu
 Val
 Asp
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 His
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 Ala
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 Arg

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 Tyr Lys Trp Phe Leu Leu Ile Tyr Lys Ile Ser Tyr Ala Thr Gly Ile
                     150
                                         155
 Val Gly Tyr Met Ala Val Met Phe Thr Leu Phe Gly Leu Asn Leu Leu
                 165
                                     170
 Phe Lys Ile Lys Pro Glu Asp Ala Met Asp Phe Gly Ile Ser Leu Leu
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                                 185
 Phe Tyr Gly Leu Tyr Tyr Gly Val Leu Glu Arg Asp Phe Ala Glu Met
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Cys Ala Asp Tyr Met Ala Ser Thr Ile Gly Phe Tyr Ser Glu Ser Gly
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Met Pro Thr Lys His Leu Ser Asp Ser Val Cys Ala Val Cys Gly Gln
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                                         235
Gln Ile Phe Val Asp Val Ser Glu Glu Gly Ile Ile Glu Asn Thr Tyr
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Arg Leu Ser Cys Asn His Val Phe His Glu Phe Cys Ile Arg Gly Trp
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Cys Ile Val Gly Lys Lys Gln Thr Cys Pro Tyr Cys Lys Glu Lys Val
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Asp Leu Lys Arg Met Phe Ser Asn Pro Trp Glu Arg Pro His Val Met
                        295
                                             300
Tyr Gly Gln Leu Leu Asp Trp Leu Arg Tyr Leu Val Ala Trp Gln Pro
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Val Ile Ile Gly Val Val Gln Gly Ile Asn Tyr Ile Leu Gly Leu Glu
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Met Leu Asp Leu Gln Lys Gln Leu Gly Arg Xaa Gln Xaa Ala Xaa Phe
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agc Ser	acc Thr	tca Ser 35	Pro	acc Thr	act Thr	gct Ala	gcg Ala 40	gcc Ala	act Thr	atg Met	cct Pro	gtg Val 45	gtg Val	ccc Pro	tct Ser	144
gtg Val	gcc Ala 50	Ser	ctg Leu	gcc Ala	cct Pro	ccg Pro 55	ggg Gly	gag Glu	gcc Ala	tcg Ser	ctc Leu 60	tgc Cys	ctg Leu	gaa Glu	gag G1u	192
gtg Val 65	gcc Ala	ccc Pro	cct Pro	gcc Ala	agt Ser 70	999 Gly	acc Thr	cgc Arg	aaa Lys	gct Ala 75	cgg Arg	gtg Val	ctc Leu	tat Tyr	gac Asp 80	240
tac Tyr	gag Glu	gca Ala	gcc Ala	gac Asp 85	agc Ser	agt Ser	gag Glu	ctg Leu	gcc Ala 90	ctg Leu	ctg Leu	gct Ala	gat Asp	gag Glu 95	ctc Leu	288
atc Ile	act Thr	gtc Val	tac Tyr 100	agc Ser	ctg Leu	cct Pro	ggc Gly	atg Met 105	gac Asp	cct Pro	gac Asp	tgg Trp	ctc Leu 110	att Ile	ggc Gly	336
gag Glu	aga Arg	ggc Gly 115	aac Asn	aag Lys	aag Lys	ggc Gly	aag Lys 120	gtc Val	cct Pro	gtc Val	acc Thr	tac Tyr 125	ttg Leu	gaa Glu	ctg Leu	384
ctc Leu	_	tag *														393
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 Ser Thr Ser Pro Thr Thr Ala Ala Ala Thr Met Pro Val Val Pro Ser
Val Ala Ser Leu Ala Pro Pro Gly Glu Ala Ser Leu Cys Leu Glu Glu
                       55
Val Ala Pro Pro Ala Ser Gly Thr Arg Lys Ala Arg Val Leu Tyr Asp
                                       75
Tyr Glu Ala Ala Asp Ser Ser Glu Leu Ala Leu Leu Ala Asp Glu Leu
               85
                                   90
Ile Thr Val Tyr Ser Leu Pro Gly Met Asp Pro Asp Trp Leu Ile Gly
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Glu Arg Gly Asn Lys Lys Gly Lys Val Pro Val Thr Tyr Leu Glu Leu
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Leu Ser
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                                                                   96
Xaa Leu Gly Gly Val Ala Glu Gly Pro Gly Leu Ala Phe Ser Glu Asp
            20
gtg ctg agc gtg ttc ggc gcg aat ctg agc ctg tcg gcg gcg cag ctc
                                                                  144
Val Leu Ser Val Phe Gly Ala Asn Leu Ser Leu Ser Ala Ala Gln Leu
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		35	5				40)				45	5				
cag Gln	cac His 50	Leu	ıctg Lev	ıgaçı Glu	g cag ıGlr	atg Met 55	: Gly	agco Ala	gco Ala	tco Ser	cgc Arg	y Val	g gg(gto / Val	c ccg I Pro		192
gag Glu 65	cct Pro	ggc Gly	cag Gln	ctg Leu	r cac His	Phe	aac Asn	cag Gln	tgt Cys	tta Leu 75	Thr	gct Ala	gaa Glu	a gag ıGlu	atc Ile 80		240
ttt Phe	tcc Ser	ctt Leu	cat His	ggc Gly 85	Phe	tca Ser	aat Asn	gct Ala	acc Thr 90	Gln	ata Ile	acc Thr	ago Ser	tco Ser 95	aaa Lys		288
ttc Phe	tct Ser	gtc Val	atc Ile 100	Cys	cca Pro	gca Ala	gtc Val	tta Leu 105	Gln	caa G1n	ttg Leu	aac Asn	ttt Phe 110	His	cca Pro		336
tgt Cys	gag Glu	gat Asp 115	cgg Arg	ccc Pro	aag Lys	cac His	aaa Lys 120	aca Thr	aga Arg	cca Pro	agt Ser	cat His 125	tca Ser	gaa Glu	gtt Val	;	384
tgg Trp	gga Gly 130	tat Tyr	gga Gly	ttc Phe	ctg Leu	tca Ser 135	gtg Val	acg Thr	att Ile	att Ile	aat Asn 140	ctg Leu	gca Ala	tct Ser	ctc Leu		432
ctc Leu 145	gga Gly	ttg Leu	att Ile	ttg Leu	act Thr 150	cca Pro	ctg Leu	ata Ile	aag Lys	aaa Lys 155	tct Ser	tat Tyr	ttc Phe	cca Pro	aag Lys 160	2	480
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gca Ala	att Ile	ttc Phe	caa Gln 180	ctt Leu	att Ile	cca Pro	gag Glu	gca Ala 185	ttt Phe	gga Gly	ttt Phe	gat Asp	ccc Pro 190	aaa Lys	gtc Val	. 5	576
gac Asp	Ser	tat Tyr 195	gtt Val	gag Glu	aag Lys	Ala	gtt Val 200	gct Ala	gtg Val	ttt Phe	ggt Gly	gga Gly 205	ttt Phe	tac Tyr	cta Leu	6	524
ctt eu l	ttc Phe	ttt Phe	ttt Phe	gaa G1u	aga Arg	atg Met	cta Leu	aag Lys	atg Met	tta Leu	tta Leu	aag Lys	aca Thr	tat Tyr	ggt Gly	6	72

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						Lys					Ile					tgc Cys	768
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				Va1					Asp				gag Glu 285	Pro			864
			Cys										999 Gly				912
													atc Ile				960
													gga Gly				1008
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1	gtg Val	atc Ile	cta Leu 355	ctc Leu	aat Asn	gca Ala	999 Gly	atg Met 360	agc Ser	act Thr	cga Arg	caa G1n	gcc Ala 365	ttg Leu	cta Leu	ttc Phe	1104
	Asn										Gly		gct Ala				1152
ł	ttg Leu	gtg Val	ggc Gly	aac Asn	aat Asn	ttc Phe	gct Ala	cca Pro	aat Asn	att Ile	ata Ile	ttt Phe	gca Ala	ctt Leu	gct Ala	gga Gly	1200

385 390 395 400 ggc atg ttc ctc tat att tct ctg gca gat atg ttt cca gag atg aat 1248 Gly Met Phe Leu Tyr Ile Ser Leu Ala Asp Met Phe Pro Glu Met Asn 405 415 gat atg ctg aga gaa aag gta act gga aga aaa acc gat ttc acc ttc 1296 Asp Met Leu Arg Glu Lys Val Thr Gly Arg Lys Thr Asp Phe Thr Phe 420 425 ttc atg att cag aat gct gga atg tta act gga ttc aca gcc att cta 1344 Phe Met Ile Gln Asn Ala Gly Met Leu Thr Gly Phe Thr Ala Ile Leu 435 440 445 ctc att acc ttg tat gca gga gaa atc gaa ttg gag taa 1383 Leu Ile Thr Leu Tyr Ala Gly Glu Ile Glu Leu Glu * 450 <210> 62 <211> 460 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(460) <223> Xaa = Any Amino Acid <400> 62 Met Ala Pro Gly Arg Ala Val Ala Gly Leu Leu Leu Leu Ala Ala Ala 5 10 Xaa Leu Gly Gly Val Ala Glu Gly Pro Gly Leu Ala Phe Ser Glu Asp Val Leu Ser Val Phe Gly Ala Asn Leu Ser Leu Ser Ala Ala Gln Leu 40 Gln His Leu Leu Glu Gln Met Gly Ala Ala Ser Arg Val Gly Val Pro Glu Pro Gly Gln Leu His Phe Asn Gln Cys Leu Thr Ala Glu Glu Ile 70 75 Phe Ser Leu His Gly Phe Ser Asn Ala Thr Gln Ile Thr Ser Ser Lys 90 Phe Ser Val Ile Cys Pro Ala Val Leu Gln Gln Leu Asn Phe His Pro 100 105 110

Cys	Glu	Asp 115	Arg	, Pro	Lys	s His	s Lys 120	s Thr)	r Arç	g Pro	Ser	His 125		· G1u	u Val
Trp	Gly 130		· Gly	Phe	. Leu	J Ser 135		l Thr	· Ile	e Ile	e Asr 140	l Leu		Ser	Leu
Leu 145	G1y	' Leu	ı Ile	Leu	Thr 150		Leu	ı Ile	e Lys	Lys 155	Ser		Phe	Pro	Lys 160
				165					170	e Gly)	/ Thr			175	Asn
			180					185	,				190	Lys	Va7
		195					200)				205			Leu
	210					215	,				220				Gly
225					230					235					Glu 240
				245					250		Asn			255	
			260					265			His		270		•
		275					280				Lys	285			
	290					295					Ile 300				
305					310					315	Phe				320
				325					330		Gln			335	
			340					345			G1u		350		
		355					360				Gln	365			
	370					375					Leu 380				
385					390					395	Phe				400
				405					410		Phe			415	
			420					425			Thr		430		
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gtg Val	tcc Ser	ctc Leu	ttc Phe 20	Leu	cag Gln	gcc Ala	tgc Cys	ttc Phe 25	ctc Leu	acc Thr	gcc Ala	atc Ile	aac Asn 30	tac Tyr	ctg Leu	96
ctc Leu	agc Ser	agg Arg 35	cac His	atg Met	gcc Ala	cac His	aag Lys 40	agt Ser	gaa Glu	cag Gln	ata Ile	ctg Leu 45	aaa Lys	gcg Ala	gcc Ala	144
agt Ser	ctc Leu 50	cag Gln	gtt Val	ccc Pro	agg Arg	ccc Pro 55	agc Ser	cct Pro	ggc Gly	cac His	cat His 60	cat His	cca Pro	cct Pro	gct Ala	192
gtc Val 65	aaa Lys	gag Glu	atg Met	aag Lys	gag Glu 70	act Thr	cag Gln	aca Thr	gag Glu	aga Arg 75	gac Asp	atc Ile	cca Pro	atg Met	tct Ser 80	240
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									cag Gln							336
									gga Gly				tga *			378

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								cac His					192
								aga Arg 75			_		240
								ccc Pro		-	_	_	288
-	_	-	_		-	_	_	gcc Ala		_	~ ~	•	336
								gaa Glu					384
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Ser	Leu 50	Gln	Val	Pro	Arg	Pro 55	Ser	Pro	Gly	His	His 60	His	Pro	Pro	Ala	
Va1 65	Lys	Glu	Met	Lys	G1u 70	Thr	Gln	Thr	Glu	Arg 75	Asp	Ile	Pro	Met	Ser 80	
·	Ser			85		·		•	90			·		95	•	
Ser	Ser	Cys	Ser 100	Ser	Pro	Pro	Ala	Cys 105	Gln	Ala	Thr	Glu	Asp 110	Val	Asp	
Tyr	Thr	Gln 115	Val	Val	Phe	Ser	Asp 120	Pro	Gly	Glu	Leu	Lys 125	Asn	Asp	Ser	
	Leu 130					135					140					
145	Pro				150					155		Val	Asn	Pro	Ala 160	
Leu	Ser	Glu	Pro	A1a 165	Glu	Tyr	Asp	Gln	Val 170	Ala	Met					
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	gcc Ala	Пe	_	Leu	-	Pro	Glu		Āla		-	Tyr			_	96
	cag Gln															144
	gaa Glu															192

	Ser											cag Gln			gac Asp 80	240
												ctg Leu			Pro	288
												gcc Ala				336
												cgc Arg 125				∵384
	cgc Arg 130	tga *														393
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_	Ala	Пе	Cys 20	-	Leu	Pro	Glu	Arg 25		Ser	Ala	Tyr	Asn 30		Arg	
Ala	G1n	Ala 35	Arg	Arg	Leu	G1n	Gly 40	Asp	Val	Ala	Gly	Ala 45	Leu	G1u	Asp	
Leu	Glu 50		Ala	Val	Glu	Leu 55		Gly	Gly	Arg	Gly 60	Arg	Ala	Ala	Arg	
G1n 65	Ser	Phe	Val	Gln	Arg 70	Gly	Leu	Leu	Ala	Arg 75	Leu	Gln	Gly	Arg	Asp 80	
	Asp	Ala		Arg 85		Phe	Glu	Arg	A1a 90		Arg	Leu	Gly	Ser 95		
Phe	Ala	Arg			Leu	Val	Leu	Leu 105		Pro	Tyr	Ala	Ala 110		Cys	
Asn	Arg	Met 115	Leu	Ala	Asp		Met 120		Gln	Leu	Arg	Arg 125		Arg	Asp	

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					tgc Cys								192
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                            40
Asn Pro Ser Glu Gln Cys Cys Tyr Asp Asp Ala Ile Leu Ser Leu Lys
Glu Thr Arg Arg Cys Gly Ser Thr Cys Thr Phe Trp Pro Cys Phe Glu
Leu Cys Cys Pro Glu Ser Phe Gly Pro Gln Gln Lys Phe Leu Val Lys
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                                    90
Leu Arg Val Leu Gly Met Lys Ser Gln Cys His Leu Ser Pro Ile Ser
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                                     10
ctg ggt gcg cct gtg gag gga gaa gcc aag cat tgg gag cct ttc cgg
                                                                       96
Leu Gly Ala Pro Val Glu Gly Glu Ala Lys His Trp Glu Pro Phe Arg
             20
aag gtg gtg tcc ggg agg atc atc aac ggc tac tgc agg gga gac tgg
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Lys	Val	Va1 35	Ser	Gly	Arg	Ile	I1e 40	Asn	Gly	Tyr	Cys	Arg 45	Gly	Asp	Trp	
			ttc Phe													192
	Leu		ccc Pro													240
			gtg Val													288
			aag Lys 100													336
			ttg Leu													384
			gct Ala										-	-		432
			ggt Gly													480
			agc Ser													528
			ctt Leu 180													576
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aag	acc	cag	ggc	ССС	agc	acg	ggg	ctg	gac	tga						657

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Lys Thr Gln Gly Pro Ser Thr Gly Leu Asp

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										ctg Leu				144
										gct Ala				192
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										aac Asn				288
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Glu Ala Lys Leu Tyr Gly Arg Cys Glu Leu Ala Arg Val Leu His Asp
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Phe Gly Leu Asp Gly Tyr Arg Gly Tyr Ser Leu Ala Asp Trp Val Cys
                            40
Leu Ala Tyr Phe Thr Ser Gly Phe Asn Ala Ala Ala Leu Asp Tyr Glu
                        55
Ala Asp Gly Ser Thr Asn Asn Gly Ile Phe Gln Ile Asn Ser Arg Arg
                    70
                                         75
Trp Cys Ser Asn Leu Thr Pro Asn Val Pro Asn Val Cys Arg Met Tyr
                85
                                     90
Cys Ser Asp Leu Leu Asn Pro Asn Leu Lys Asp Thr Val Ile Cys Ala
                                105
Met Lys Ile Thr Gln Glu Pro Gln Gly Leu Gly Tyr Trp Glu Ala Trp
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Arg His His Cys Gln Gly Lys Asp Leu Thr Glu Trp Val Asp Gly Cys
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Asp Phe
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Met Leu Cys Phe Leu Arg Gly Met Ala Phe Val Pro Phe Leu Leu Val
1
                 5
                                     10
                                                          15
acc tgg tcg tca gcc gcc ttc att atc tcc tac gtg gtc gcc gtg ctc
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Thr	Trp	Ser	Ser 20	Ala	Ala	Phe	Ile	Ile 25	Ser	Tyr	Val	Val	Ala 30	Val	Leu	
			gtc Val					_			-		_			144
			gag Glu	-						_					-	192
			gca Ala											_	_	240
			acc Thr							_			-			288
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	cag Gln	tga *														345
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Met 1		l00> Cys	76 Phe	Leu 5	Arg	Gly	Met	Ala	Phe 10	Val	Pro	Phe	Leu	Leu 15	Val	
Thr	Trp	Ser	Ser 20	Ala	Ala	Phe	Ile	I1e 25		Tyr	Val	Val	Ala 30	-	Leu	
	-	35	Val				40		·			45		•		
	50		Glu			55		-			60					
Phe 55	Leu	Gly	Ala		Thr 70	Met	fyr	Thr		Tyr 75	Lys	Ile	Val	Gln	Lys 80	

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								ctg Leu						38	34
								aac Asn			_		-	43	32
	_		-	-	_	-		gta Val 155	-	_	-	-	_	48	30
								ctg Leu						52	28
								cat His		_	_	-	-	57	'6
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								ctc Leu						67	'2
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Val				Ala				ttc Phe						86	4

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Leu	Ala	Arg 35	Arg	Arg	Lys	Lys	I1e 40	Leu	Phe	Tyr	Cys	His 45	Phe	Pro	Asp	
Leu	Leu 50	Leu	Thr	Lys	Arg	Asp 55	Ser	Phe	Leu	Lys	Arg 60	Leu	Tyr	Arg	Ala	
Pro 65	Ile	Asp	Trp	Ile	G1u 70	Glu	Tyr	Thr	Thr	Gly 75	Met	A] a	Asp	Cys	I1e 80	
Leu	Val	Asn	Ser	G1n 85	Phe	Thr	Ala	Ala	Val 90	Phe	Lys	Glu	Thr	Phe 95	Lys	
Ser	Leu	Ser	His 100	Пe	Asp	Pro	Asp	Val 105	Leu	Tyr	Pro	Ser	Leu 110	Asn	Val	
Thr	Ser	Phe 115	Asp	Ser	Val	Val	Pro 120	Glu	Lys	Leu	Asp	Asp 125		Val	Pro	
Lys	Gly 130	Lys	Lys	Phe	Leu	Leu 135		Ser	Ile	Asn	Arg 140		Glu	Arg	Lys	
	Asn	Leu	Thr	Leu		Leu	Glu	Ala	Leu		Gln	Leu	Arg	Gly	Arg	
145	Thus	Care	07.4	۸	150	01.		V . 7		155				0.7	160	
			Gln	165					170					175		
Tyr	Asp	Glu	Arg	Val	Leu	Glu	Asn	۷a٦	Glu	His	Tyr	Gln	Glu	Leu	Lys	

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                                                 205
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                                            220
Val Leu Tyr Thr Pro Ser Asn Glu His Phe Gly Ile Val Pro Leu Glu
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                                        235
Ala Met Tyr Met Gln Cys Pro Val Ile Ala Val Asn Ser Gly Gly Pro
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                                    250
Leu Glu Ser Ile Asp His Ser Val Thr Gly Phe Leu Cys Glu Pro Asp
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                                265
Pro Val His Phe Ser Glu Ala Ile Glu Lys Phe Ile Arg Glu Pro Ser
                            280
Leu Lys Ala Thr Met Gly Leu Ala Gly Arg Ala Arg Val Lys Glu Lys
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		Leu									gag Glu 60					192
999 Gly 65	۷a٦	ggc Gly	gag Glu	ctc Leu	ata Ile 70	۷al	cgg Arg	gag Glu	ctg Leu	gac Asp 75	ctc Leu	gcc Ala	tcg Ser	ctg Leu	cgc Arg 80	240
tcg Ser	gtg Val	cgc Arg	gcc Ala	ttc Phe 85	tgc Cys	cag Gln	gaa Glu	atg Met	ctc Leu 90	cag Gln	gaa G1u	gag Glu	cct Pro	agg Arg 95	ctg Leu	288
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											aac Asn					384
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cgc Arg	cgc Arg	tta Leu	gaa Glu	ggc Gly	aca Thr	aat Asn	gtc Val	acc Thr	gtc Val	aat Asn	gtg Val	ttg Leu	cat His	cct Pro	ggt Gly	624

		195					200					205				
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Asp Val Leu Ile Asn Asn Ala Gly Ile Phe Gln Cys Pro Tyr Met Lys
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Thr Glu Asp Gly Phe Glu Met Gln Phe Gly Val Asn His Leu Gly His
Phe Leu Leu Thr Asn Leu Leu Leu Gly Leu Leu Lys Ser Ser Ala Pro
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Ser Arg Ile Val Val Ser Ser Lys Leu Tyr Lys Tyr Gly Asp Ile
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Asn Phe Asp Asp Leu Asn Ser Glu Gln Ser Tyr Asn Lys Ser Phe Cys
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Tyr Ser Arg Ser Lys Leu Ala Asn Ile Leu Phe Thr Arg Glu Leu Ala
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Arg Arg Leu Glu Gly Thr Asn Val Thr Val Asn Val Leu His Pro Gly
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Ile Val Arg Thr Asn Leu Gly Arg His Ile His Ile Pro Leu Leu Val
                        215
Lys Pro Leu Phe Asn Leu Val Ser Trp Ala Phe Phe Lys Thr Pro Val
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Glu Gly Ala Gln Thr Ser Ile Tyr Leu Ala Ser Ser Pro Glu Val Glu
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144	atc Ile				ttg Leu			Pro					Asp			
192					gaa Glu 60											
240					gtt Val											
288	agt Ser	ggc Gly 95	aca Thr	agt Ser	aat Asn	cca Pro	aca Thr 90	cct Pro	act Thr	cag Gln	cat His	cat His 85	gga Gly	ttg Leu	acc Thr	gct Ala
336					cca Pro											
384					tcc Ser											
432					ggc Glу 140											
480		Ser			ctg Leu											
528			Leu		gaa Glu											
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														ctt Leu		672
														tta Leu		720
														att Ile 255		768
														tgg Trp		816
														aag Lys		864
														tta Leu		912
														gtt Val		960
			Lys					Phe						tcc Ser 335		1008
		Pro					Tyr							aag Lys		1056
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	p G1					Thr					Tyr				atc Ile 400	1200
					gtg Val					Glu					Cys	1248
				Tyr	agt Ser											1296
			/ Lys		cac His											1344
		s Lys			tgc Cys											1392
	r Ala				aca Thr 470											1440
					aag Lys											1488
gaq G1u	g tai u Tyr	gaa Glu	tcc Ser 500	cgc Arg	agc Ser	ctt Leu	tgg Trp	aag Lys 505	gat Asp	gtc Val	act Thr	ttc Phe	aac Asn 510	tta Leu	aaa Lys	1536
			Пe		gca Ala	Ala										1584
aga	a caa	aga	gca	gaa	gcc	cga	gaa	agg	aag	gag	aag	gaa	att	cag	tgg	1632

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	ı Thr					Glu					Trp				gaa Glu 560	1680
					ctt Leu					His						1716
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Ser	Thr 50	Met	Pro	Ser	G1n	Thr 55		Leu	Pro	Pro	Glu 60		Val	Gln	Leu	
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Ala	Thr	Leu	Gly	His 85	His	Gln	Thr	Pro	Thr 90	Pro	Asn	Ser	Thr	Gly 95		
Gly	His	Ser	Pro 100	Pro	Ser	Ser	Ser	Leu 105	Thr	Ser	Pro	Ser	His 110	Val	Asn	
Leu	Ser	Pro 115	Asn	Thr	Val	Pro	Glu 120	Phe	Ser	Tyr	Ser	Ser 125	Ser	Glu	Asp	
Glu	Phe 130	Tyr	Asp	Ala	Asp	G1u 135	Phe	His	Gln	Ser	Gly 140		Ser	Pro	Lys	
Arg 145	Leu	Ile	Asp	Ser	Ser 150	Gly	Ser	Ala	Ser	Val 155	Leu	Thr	His	Ser	Ser 160	
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Ser	Leu	Ser	Asn 180		Thr	Ser	Asp	Ala 185		Leu	Phe	Asp	Ser 190		Asp	
Asp	Arg	Asp 195		Asp	Ala		Ala 200		Ser	Val	G1u	G1u 205		Lys	Ser	

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Lys 225		Val	Leu	Pro	Thr 230		Ile	Leu	Glu	Arg 235		Ser	Leu	Leu	G1u 240
Met	Tyr	Ala	Asp	Phe 245		Ala	His	Pro	Asp 250		Phe	۷a٦	Ser	Ile 255	Ser
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Asn 305	Asp	Thr	Glu	Glu	Asn 310	Thr	Glu	Leu	۷a٦	Ser 315	Glu	Gly	Pro	Val	Pro 320
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Ser	Lys	Thr	Gly 420	Tyr	Ser	Ala	Asn	Ile 425	Ile	Phe	His	Thr	Lys 430	Pro	Phe
Tyr	Gly	Gly 435	Lys	Lys	His	Arg	Ile 440	Thr	Ala	Glu	Ile	Phe 445	Ser	Pro	Asn
Asp	Lys 450	Lys	Ser	Phe	Cys	Ser 455	Ile	Glu	Gly	Glu	Trp 460	Asn	Gly	Val	Met
Tyr 465	Ala	Lys	Tyr	Ala	Thr 470	Gly	Glu	Asn	Thr	Val 475	Phe	Val	Asp	Thr	Lys 480
Lys	Leu	Pro	Ile	Ile 485	Lys	Lys	Lys	Val	Arg 490		Leu	Glu	Asp	G1n 495	Asn
Glu	Tyr	Glu	Ser 500	Arg	Ser	Leu	Trp	Lys 505	Asp	Val	Thr	Phe	Asn 510	Leu	Lys
He	Arg	Asp 515	Ile	Asp	Ala	Ala	Thr 520	Glu	Ala	Lys	His	Arg 525		Glu	Glu
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						aag Lys							288
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Thr	Asn 50	Lys	Arg	Lys		Tyr 55	Ser	G1u	Arg		Ile 60		Gly	Tyr	Ser	
1et 55	Gln	Glu	Met			Va1	Val	Ser				Glu	Tyr	Arg	Glu 80	
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His	Leu	Lys	Ala 100		Leu	ı Glu	ı Val	ر G1 105		Pro) Pro	Va]	Met 110		ı Arg	
Tyr	Thr	Ser 115		Val	Ser	Met	: Val 120		Pro	His	Met	Val 125	Lys		a Val	
Cys	Thr 130		G1y	Lys	Leu	Phe	Asr		Leu	ı Glu	Thr 140	Ile		Arg) Phe	
Ser 145		Gly	Ile	Р́го	Ala 150	Tyr		Arg	Thr	Cys 155	Thr		Asp) Phe	Ser 160	
Ile	Ser	Phe	Glu	Phe 165	Arg		Leu	Leu	His 170	Ser		Leu	ı Ala	Thr 175	Met	
Phe	Phe	Asp	Glu 180		Val	Lys	G1n	Asn 185	Val		Ala	Phe	Glu 190	ı Arg	Arg	
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cag	gag	tat	cgt	gag	ttt	gtg	ССС	tgg	tgt	aag	aag	tct	ctg	gtg	gta	240

G1r 65	Glu	Tyr	Arg	Glu	Phe 70		Pro	Trp	Cys	Lys 75		Ser	· Lei	ı Val	Va1 80	
															cca Pro	288
	gtc Val			Arg					Val					Pro		336
	gtc Val		Ala										His			384
	att Ile 130															432
act Thr 145	gtg Val	gac Asp	ttt Phe	tcg Ser	att Ile 150	tcc Ser	ttt Phe	gaa Glu	ttt Phe	cgt Arg 155	tct Ser	ctg Leu	ctg Leu	cac His	tcc Ser 160	480
cag G1n	ctg Leu	gcc Ala	acc Thr	atg Met 165	ttt Phe	ttt Phe	gat Asp	gag Glu	gtt Val 170	gtc Val	aaa Lys	cag Gln	aat Asn	gtt Val 175	gct Ala	528
gcc Ala	ttt Phe	gag Glu	cgt Arg 180	cgg Arg	gca Ala	gcc Ala	acc Thr	aag Lys 185	ttt Phe	ggt Gly	cca Pro	gaa Glu	aca Thr 190	gcc Ala	atc Ile	576
	cgt Arg											tga *				615
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Phe	Ala	A1a 35	Pro	Phe	Thr	Asn	Lys 40		Lys	Ala	Tyr	Ser 45		Arg	Arg	
Ile	Met 50	Gly	Tyr	Ser	Met	G1n 55	Glu	Met	Tyr	Glu	Val 60	Val	Ser	Asn	Val	÷
65					70	Val				75					80	
Ser	Ser	Arg	Lys	G1 <i>y</i> 85	His	Leu	Lys	Ala	G1n 90	Leu	Glu	Val	Gly	Phe 95	Pro	
			100			Thr		105					110			
		115				Thr	120					125				
	130					Pro 135					140				_	
145					150	Ser				155					160	
				165		Phe			170					175		
Ala	Phe	Glu	Arg 180	Arg	Ala	Ala	Thr	Lys 185	Phe	Gly	Pro	Glu	Thr 190	Ala	Ile	
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gcc Ala	gct Ala	gtt Val	gtc Val 20	agg Arg	tgc Cys	cag Gln	gag Glu	cag Gln 25	gcc Ala	cag G1n	acc Thr	acc Thr	gac Asp 30	tgg Trp	aga Arg	96
gcc	acc	ctg	aag .	acc	atc	cgg	aac	ggc	gtt	cat	aag	ata	gac	acg	tac	144

Ala	Thr	Leu 35		Thr	Пe	Arg	Asn 40		Val	His	Lys	Ile 45	Asp	Thr	Tyr	
															cag Gln	192
tat Tyr 65	aaa Lys	tgc Cys	agt Ser	gac Asp	gga Gly 70	tct Ser	aag Lys	cct Pro	ttc Phe	cca Pro 75	cgt Arg	tat Tyr	ggt Gly	tat Tyr	aaa Lys 80	240
			ccg Pro													288
			atc Ile 100													336
			acc Thr													384
			ctc Leu													432
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Ala	Thr	Leu 35	Lys	Thr	Ile	Arg	Asn 40	Gly	Val	His	Lys	Ile 45	Asp	Thr	Tyr	
Leu	Asn 50	Ala	Ala	Leu	Asp	Leu 55	Leu	Gly	Gly	Glu	Asp 60	Gly	Leu	Cys	G1n	
65	Lys				70					75		-	•	-	80	
Pro	Ser	Pro	Pro	Asn 85	Gly	Cys	Gly	Ser	Pro 90	Leu	Phe	Gly	Val	His 95	Leu	
Asn	Ile	Gly	Ile 100	Pro	Ser	Leu	Thr	Lys 105	Cys	Cys	Asn	Gln	His 110	Asp	Arg	
Cys	Tyr	G1u 115	Thr	Cys	Gly	Lys	Ser 120	Lys	Asn	Asp	Cys	Asp 125	Glu	Glu	Phe	
	Tyr 130					135					140				•	
145	Thr				150					155					160	
	Ser			165					170				Ser	Gln 175	Arg	
Ala	Ala	Cys	Arg 180	Cys	His	Tyr	Glu	Glu 185	Lys	Thr	Asp	Leu				
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gtg Val	atc Ile	cag G1n	gtg Val 20	ttc Phe	cag Gln	cag G1n	ctg Leu	ggc Gly 25	tgt Cys	gcg Ala	gtg Val	att Ile	gac Asp 30	gtg Val	gac Asp	96

			Arg									gcc Ala 45			cgc Arg	144
												Asn			ata Ile	192
												cct Pro				240
												aag Lys				288
												tac Tyr				336
												aag Lys 125				384
												ctg Leu				432
												gcc Ala				480
												cgc Arg				528
gac Asp	aac Asn	tcg Ser	ggc Gly 180	gag Glu	tgg Trp	agt Ser	gtc Val	acc Thr 185	aaa Lys	cgc Arg	cag Gln	gtc Val	atc Ile 190	ctc Leu	ttg Leu	576
	Thr					Ser						ctg Leu 205				624

gtc Val	ctc Leu 210	Thr	999 Gly	ctc Leu	gct Ala	gcc Ala 215	IJе	gcc Ala	ago Ser	cto Leu	cto Leu 220	ı Tyr	ctg Leu	ctc Leu	acc Thr	672
	Tyr		ctg Leu			Ala		!								696
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Val	Ile	Gln	Va1 20	Phe	Gln	Gln	Leu	Gly 25		Αla	۷a٦	Ile	Asp 30		Asp	
Val	Met	A1a 35	Arg	His	Val	Val	Gln 40	Pro	Gly	Tyr	Pro	Ala 45	His	Arg	Arg	
Ile	Va1 50	Glu	Val	Phe	Gly	Thr 55	Glu	Val	Leu	Leu	G1u 60		Gly	Asp	Ile	
Asn 65	Arg	Lys	Val	Leu	G1 <i>y</i> 70	Asp	Leu	Пe	Phe	Asn 75	G1n	Pro	Asp	Arg	Arg 80	
Gln	Leu	Leu	Asn	A1a 85	Ile	Thr	His	Pro	G1u 90		Arg	Lys	Glu	Met 95		
_ys	Glu	Thr	Phe 100		Tyr	Phe	Leu	Arg 105		Tyr	Arg	Tyr	Val 110		Leu	
₹sp	Ile	Pro 115	Leu	Leu	Phe	Glu	Thr 120		Lys	Leu	Leu	Lys 125		Met	Lys	
lis	Thr 130	Val	Val	Val	Tyr	Cys 135	Asp	Arg	Asp	Thr	G1n 140	Leu	Ala	Arg	Leu	
1et 145	Arg	Arg	Asn	Ser	Leu 150	Asn	Arg	Lys	Asp	Ala 155	Glu	Ala	Arg	Ile	Asn 160	
\1a	Gln	Leu	Pro	Leu 165	Thr	Asp	Lys	Ala	Arg 170	Met	Ala	Arg	His	Val 175	Leu	
sp	Asn	Ser	Gly 180	Glu	Trp	Ser	Val	Thr 185	Lys	Arg	Gln	Val	Ile 190	Leu	Leu	
lis		Glu 195	Leu	Glu	Arg	Ser	Leu 200		Tyr	Leu	Pro	Leu 205		Phe	Gly	
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Met Asp Ala Leu Ala Leu Leu Gly Gly Leu Val Asn Xaa Ala Arg Leu
 1
                 5
                                                           15
ccc gag cgc tgg gga cct ggc cgc ttt gac tac tgg ggc aac tcc cac
                                                                        96
Pro Glu Arg Trp Gly Pro Gly Arg Phe Asp Tyr Trp Gly Asn Ser His
             20
cag atc atg cac ctg ctg agc gtg ggc tcc atc ctg cag ctg cac gcc
                                                                       144
Gln Ile Met His Leu Leu Ser Val Gly Ser Ile Leu Gln Leu His Ala
         35
ggc gtc gtg ccc gac ctg ctc tgg gct gcc cac cac gcc tgt ccc cgg
                                                                       192
Gly Val Val Pro Asp Leu Leu Trp Ala Ala His His Ala Cys Pro Arg
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gac tga
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Asp *
65
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 Gln Ile Met His Leu Leu Ser Val Gly Ser Ile Leu Gln Leu His Ala
 Gly Val Val Pro Asp Leu Leu Trp Ala Ala His His Ala Cys Pro Arg
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                                      10
agg cac agc cta ttg tct cct ttg ctc agt gtg aca tca ttc aga cgc
                                                                       96
Arg His Ser Leu Leu Ser Pro Leu Leu Ser Val Thr Ser Phe Arg Arg
             20
                                  25
ttc tac aga ggt gac agc cca aca gat tcc caa aag gac atg att gaa
                                                                      144
Phe Tyr Arg Gly Asp Ser Pro Thr Asp Ser Gln Lys Asp Met Ile Glu
         35
atc cct ttg cct cca tgg cag gag aga act gat gaa tcc ata gaa acc
                                                                      192
Ile Pro Leu Pro Pro Trp Gln Glu Arg Thr Asp Glu Ser Ile Glu Thr
     50
                         55
                                             60
aaa aga gcc cgc ctg ctc tat gag agc aga aag agg gga atg ttg gaa
                                                                      240
Lys Arg Ala Arg Leu Leu Tyr Glu Ser Arg Lys Arg Gly Met Leu Glu
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							455							
65			70					75	5				80	
aac tgc Asn Cys	att ct Ile Le	t ctt u Leu 85	ı Ser	ctt Leu	ttt Phe	get Ala	t aaa A Lys 90	G]ı	a cat i His	t ctg s Lei	cag ıGlr	cad His	Met	288
aca gaa Thr Glu	aag ca Lys Gl 10	n Leu	aac Asn	ctc Leu	tat Tyr	gac Asp 105	Arg	ctg Leu	ıatt ıIle	aac Asr	gag Glu 110	Pro	agt Ser	336
aat gac Asn Asp	tgg ga Trp As 115	t att p Ile	tac Tyr	tac Tyr	tgg Trp 120	Ala	aca Thr	gaa Glu	gct Ala	aaa Lys 125	Pro	gcc Ala	cca Pro	384
gaa ata Glu Ile 130	Phe G1	a aat u Asn	gaa Glu	gtc Val 135	atg Met	gcc Ala	ctg Leu	ctg Leu	aga Arg 140	Asp	ttt Phe	gct Ala	aaa Lys	432
aac aaa Asn Lys 145	aac aa Asn Ly	a gag s Glu	cag Gln 150	aga Arg	ctg Leu	cgt Arg	gcc Ala	cca Pro 155	gat Asp	ctt Leu	gag Glu	tac Tyr	ctc Leu 160	480
ttt gaa Phe Glu														498
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Phe Tyr	20 Arg Gly 35	Asp	Ser			25 Asp	Ser	Gln	Lys		30 Met	Пе	Glu	
Ile Pro 50		Pro				Arg	Thr	Asp	G1u 60	45 Ser	Ile	Glu	Thr	
Lys Arg 65	Ala Arg	Leu			Glu	Ser	Arg	Lys 75		Gly	Met		Glu 80	
Asn Cys	Ile Leu	Leu	Ser 1	Leu I	Phe	Ala	Lys	Glu	His	Leu	Gln			

				85					90					95		
Thr	Glu	ı Lys	G]r 100	n Lei	ı Asr	n Leu	ı Tyr	Asp 105	Arg	J Lei	ı Ile	e Asr	1 Glu	ı Pro	Ser	
Asr	ı Asp	Trp 115) Ile	e Tyr	Tyr	Trp 120	Ala		· Glu	ı Ala	Lys 125	Pro		a Pro	
	130					135	•				140)			a Lys	
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Phe	Glu	Lys	Pro	Arg 165												
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tca Ser	agg Arg	cac His	agc Ser 20	cta Leu	ttg Leu	tct Ser	cct Pro	ttg Leu 25	ctc Leu	agt Ser	gtg Val	aca Thr	tca Ser 30	ttc Phe	aga Arg	96
cgc Arg	ttc Phe	tac Tyr 35	aga Arg	ggt Gly	gac Asp	agc Ser	cca Pro 40	aca Thr	gat Asp	tcc Ser	caa Gln	aag Lys 45	gac Asp	atg Met	att Ile	144
gaa Glu	atc Ile 50	cct Pro	ttg Leu	cct Pro	cca Pro	tgg Trp 55	cag Gln	gag Glu	aga Arg	act Thr	gat Asp 60	gaa Glu	tcc Ser	ata Ile	gaa Glu	192
acc Thr 65	aaa Lys	aga Arg	gcc Ala	cgc Arg	ctg Leu 70	ctc Leu	tat Tyr	gag Glu	agc Ser	aga Arg 75	aag Lys	agg Arg	gga Gly	atg Met	ttg Leu 80	240
gaa Glu	aac Asn	tgc Cys	att Ile	ctt Leu	ctt Leu	agt Ser	ctt Leu	ttt Phe	gct Ala	aaa Lys	gaa Glu	cat His	ctg Leu	cag Gln	cac His	288

				85					90	١				95		
				Gln					Asp					Glu	cct Pro	336
			tgg Trp					Trp					Lys			384
		Ile	ttt Phe									Arg				432
	Asn		aac Asn								Pro					480
			aag Lys			tga *										501
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Ser	Arg	His	Ser 20	Leu	Leu	Ser	Pro	Leu 25	Leu	Ser	Val	Thr	Ser 30	Phe	Arg	
Arg	Phe	Tyr 35	Arg	Gly	Asp	Ser					Gln		Asp	Met	Ile	
Glu	Ile 50	Pro	Leu	Pro	Pro	Trp 55	Gln	Glu	Arg	Thr	Asp 60	Glu	Ser	Ile	Glu	
Thr 65		Arg	Ala	Arg	Leu 70		Tyr	Glu	Ser	Arg 75		Arg	Gly	Met	Leu 80	
	Asn	Cys	Пe	Leu 85		Ser	Leu	Phe	Ala 90		Glu	His	Leu	G1n 95		
Met	Thr	Glu	Lys 100		Leu	Asn	Leu	Tyr 105		Arg	Leu	Ile	Asn 110		Pro	
Ser	Asn	Asp	Trp	Asp	Пе	Tyr	Tyr		Ala	Thr	Glu	Ala		Pro	Ala	

		118					120					125				
Pro	61ս 130		Phe	e Glu	ı Asr	Glu 135		Met	: Ala	Leu	Leu 140		l Asp	Phe	Ala	
Lys 145		Lys	Asn	Lys	Glu 150	Gln		Leu	ı Arg	Ala 155	Pro		Leu	Glu	Tyr 160	
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ggc Gly	atc Ile	aat Asn	att Ile 20	gtc Val	ttc Phe	ata Ile	cca Pro	tca Ser 25	gca Ala	tta Leu	gca Ala	gca Ala	atc Ile 30	ctt Leu	gga Gly	96
gca Ala	gtg Val	cca Pro 35	ttc Phe	ctg Leu	999 Gly	aca Thr	tac Tyr 40	tgg Trp	gca Ala	gca Ala	gta Val	cct Pro 45	gca Ala	gtt Val	ctt Leu	144
gac Asp	ctg Leu 50	tgg Trp	ctg Leu	aca Thr	caa Gln	999 Gly 55	tta Leu	gga Gly	tgc Cys	aag Lys	gcc Ala 60	att Ile	tta Leu	ctg Leu	ttg Leu	192
													atc Ile			240
gac Asp	ata Ile	tca Ser	gga Gly	ggt Gly 85	ggc Gly	cat His	cct Pro	tac Tyr	ctg Leu 90	aca Thr	ggc Gly	ttg Leu	gca Ala	gtg Val 95	gcc Ala	288
													ggt Glv			336

100 105 110 ctt ctc tgc ata ctt gtg gtt gct tcc aat atc tat agt gcc atg cta 384 Leu Leu Cys Ile Leu Val Val Ala Ser Asn Ile Tyr Ser Ala Met Leu 115 120 125 gtg agt ccc acg aat tca gtt ccc acg cca aac cag acc cca tgg cct 432 Val Ser Pro Thr Asn Ser Val Pro Thr Pro Asn Gln Thr Pro Trp Pro 135 140 gct cag cct cag cgg act ttc cgt gac att tct gaa gat ctg aaa tct 480 Ala Gln Pro Gln Arg Thr Phe Arg Asp Ile Ser Glu Asp Leu Lys Ser 145 150 155 tca gta ggt tga 492 Ser Val Gly *

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ttc Phe	ccc Pro 50	aag Lys	caa Gln	ttc Phe	aag Lys	acc Thr 55	cag Gln	caa Gln	tac Tyr	tac Tyr	aac Asn 60	gtc Val	ctg Leu	aag Lys	cag G1n	192
														agt Ser		240
agg Arg	ctc Leu	cca Pro	gat Asp	ctg Leu 85	acc Thr	aca Thr	gtc Val	atc Ile	tcg Ser 90	gtg Val	gat Asp	gcc Ala	cct Pro	ttg Leu 95	ccg Pro	288
ggg Gly	acc Thr	ctg Leu	ctc Leu	ctg Leu	gat Asp	gaa Glu	gtg Val	gtg Val	gcg Ala	gct Ala	ggc Gly	agc Ser	aca Thr	cgg Arg	cag Gln	336

		100				105			110		
		Gln							Cys	gac Asp	384
	Asn			acc Thr 135				Ser			432
				aac Asn							480
				gag Glu						atc Ile	528
				cat His							576
				gcc Ala							624
				gag Glu 215							672
				atg Met							720
				tcg Ser							768
				ttg Leu	Пe						816
				gct Ala							864

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gtg ggc Val Gly 305	aga att Arg Ile	atg cct Met Pro 310	cac a His T	icg gag Thr Glu	gcc Ala	cgg Arg 315	atc Ile	atg Met	aac Asn	atg Met	gag Glu 320	960
gca ggg Ala Gly	acg ctg Thr Leu	gca aag Ala Lys 325	ctg a Leu A	ac acg sn Thr	ccc Pro 330	ggg Gly	gag Glu	ctg Leu	tgc Cys	atc Ile 335	cga Arg	1008
ggg tac Gly Tyr	tgc gtc Cys Val 340	atg ctg Met Leu	ggc t Gly T	ac tgg yr Trp 345	ggt Gly	gag Glu	cct Pro	cag Gln	aag Lys 350	aca Thr	gag Glu	1056
gaa gca Glu Ala			Lys T									1104
atg aat Met Asn 370	gag cag Glu G ln	ggc ttc Gly Phe	tgc a Cys L 375	ag atc ys Ile	gtg Val	ggc Gly	cgc Arg 380	tct Ser	aag Lys	gat Asp	atg Met	1152
atc atc Ile Ile / 385	cgg ggt Arg Gly	ggt gag Gly Glu 390	aac a Asn I	tc tac le Tyr	ccc Pro	gca Ala 395	gag Glu	ctc Leu	gag Glu	Asp	ttc Phe 400	1200
ttt cac a	aca cac Thr His	ccg aag Pro Lys 405	ntg ca Xaa G	ag gaa In Glu	gtg Val 410	cag Gln	gtg Val	gtg Val	Gly	gtg Val 415	aag Lys	1248
gac gat o Asp Asp A	atg atg Arg Met 420	ggg gaa Gly Glu	gag at Glu II	tt tgt Ie Cys 425	gcc Ala	tgc Cys	att Ile	Arg	ctg Leu 430	aag Lys	gac Asp	1296
ggg gag g Gly Glu G				lu Ile			Phe					1344
atc tct c Ile Ser H	ac ttc lis Phe	aag att Lys Ile	ccg aa Pro Ly	ng tac vs Tyr	atc Ile	gtg Val	ttt Phe	gtc Val	aca Thr	aac Asn	tac Tyr	1392

450 455 460

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1464

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165

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170

Leu	Pro	Asn	Pro 180		Tyr	His	Cys	Leu 185		Ser	Val	Ala	Gly 190	Thr	Met
		195					200					205		lle	
	210					215					220		_	Thr	
225					230					235				Pro	240
				245					250					Ala 255	
			260					265					270		
		275					280					285		Pro	
	290					295					300			Glu	
305					310					315				Met	320
				325					330					Ile 335	_
			340					345					350	Thr	
		355					360					365		Ala	
	370					375					380			Asp	
385					390					395				Asp	400
				405					410					Val 415	
			420					425					430	Lys	•
		435					440					445		Gly	
	450					455		-			460			Asn	Ū
465					470		He	Gln	Lys	Phe 475	Lys	Leu	Arg	Glu	G1n 480
Met	Glu	Arg		Leu 485	Asn	Leu									

<210> 101

<211> 348

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			att Ile 20													96
			999 Gly													144.
ccc Pro	tgg Trp 50	gct Ala	ctg Leu	cag Gln	acc Thr	ctg Leu 55	gct Ala	gtg Val	gat Asp	tac Tyr	gga Gly 60	tcc Ser	tac Tyr	atc Ile	cgg Arg	192
			agg Arg						Val							240
			acg Thr													288
			ggc Gly 100													336
tct Ser	cca Pro		tga *													348
	<2 <2	210> 211> 212> 213>	115	sap	iens											

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Ala	Ser	Leu	Ile 20	Val	Ala	Arg	Gln	Gly 25	Met	Gly	Asp	Met	Ala 30		Ser	
Asn	Ser	I1e 35	Gly	Ser	Asn	Val	Phe 40	Asp	Ile	Leu	Ile	Gly 45		Gly	Leu	
Pro	Trp 50	Ala	Leu	Gln	Thr	Leu 55	Ala	Val	Asp	Tyr	Gly 60	Ser	Tyr	Ile	Arg	
Leu 65	Asn	Ser	Arg	Gly	Leu 70	He	Tyr	Ser	Val	G1y 75	Leu	Leu	Leu	Ala	Ser 80	•
Val	Phe	Val	Thr	Va1 85	Phe	Gly	Val	His	Leu 90	Asn	Lys	Trp	Gln	Leu 95	Asp	
Lys	Lys	Leu	Gly 100	Cys	Gly	Cys	Leu	Leu 105	Leu	Tyr	Gly	Cys	Ser 110	Cys	Ala	
Ser	Pro	Ser 115														
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ata		<000		ata	992	o+a	202	++~	+ = =	~~~	005		·	~+~		40
				gtg Val 5												48
				cga Arg												96
gac Asp	agc Ser	ctc Leu 35	ttc Phe	atc Ilė	tať Tyr	gac Asp	tgc Cys 40	agt Ser	gct Ala	gca Ala	gaa Glu	aag Lys 45	aag Lys	tca Ser	caa Gln	144
gaa Glu	aat Asn 50	aaa Lys	999 Gly	gag Glu	gac Asp	gcg Ala 55	ccc Pro	ttg Leu	gac Asp	cag Gln	999 Gly 60	agc Ser	ggt Gly	gcg Ala	att Ile	192

					tcc Ser 70	Lys					Phe					240
					att Ile					Lys					Leu	288
				Val	gca Ala				Thr					Пe		336
			Lys		ttg Leu			Asp								384
					cca Pro											432
ctg Leu 145	tct Ser	atg Met	ctg Leu	tta Leu	gat Asp 150	gtg Val	gct Ala	gtg Val	agt Ser	cct Pro 155	gat Asp	gac Asp	cgc Arg	ttc Phe	atc Ile 160	480
					gac Asp											528
ccc Pro	cat His	agc Ser	atc Ile 180	gag Glu	tcc Ser	ttc Phe	tgc Cys	ttg Leu 185	999 Gly	cac His	aca Thr	gag Glu	ttt Phe 190	gtg Val	agc Ser	576
					cca Pro											624
Sly	gac Asp 210	ggc Gly	acc Thr	ctg Leu	agg Arg	ctc Leu 215	tgg Trp	gag Glu	tac Tyr	agg Arg	agc Ser 220	ggc Gly	cgc Arg	cag Gln	ctg Leu	672
cac His 225	tgc Cys	tgt Cys	cac His	ctg Leu	gcc Ala 230	agt Ser	ctg Leu	cag Gln	gag Glu	ctg Leu 235	gtg Val	gac Asp	ccc Pro	cag Gln	gcc Ala 240	720

					Ala					Phe					aac Asn	768
									Pro						cag Gln	816
			cgc Arg													864
			gtg Val													912
			gac Asp													960
			tgg Trp													1008
			ctt Leu 340													1056
			agc Ser													1104
			ctg Leu		Lys											1152
aag Lys 385	aag Lys	cag Gln	cgg Arg	cgc Arg	cgg Arg 390	agt Ser	ccc Pro	ccg Pro	cct Pro	999 Gly 395	ccc Pro	gac Asp	ggg Gly	His	gcc Ala 400	1200
			aga Arg					Thr				tga *				1239

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Gln	His 290	Gln	Val	Trp	Asp	Val 295		Phe	G1u	Glu	Thr 300		Gly	Leu	Trp	
Val 305		Gln	Asp	Cys	Gln 310		Ala	Pro	Leu	Val 315	Leu	Tyr	Arg	Pro	Val 320	
Gly	Asp	Gln	Trp	G1n 325	Ser	Val	Pro	Glu	Ser 330		Val	Leu	Lys	Lys 335		
Ser	Gly	Val	Leu 340	Arg	Gly	Asn	Trp	A1a 345		Leu	G1u	Gly	Ser 350		Gly	
Ala	Asp	A1a 355	Ser	Phe	Ser	Ser	Leu 360		Lys	Ala	Thr	Phe 365		Asn	Val	
Thr	Ser 370	Tyr	Leu	Lys	Lys	Lys 375		Glu	Arg	Leu	G1n 380	Gln	Gln	Leu	Glu	
Lys 385	Lys	Gln	Arg	Arg	Arg 390	Ser	Pro	Pro	Pro	G1y 395	Pro	Asp	Gly	His	Ala 400	
Lys	Lys	Met	Arg	Pro 405	Gly	Glu	Ala	Thr	Leu 410	Ser	Cys					
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											Leu					40
tta Leu	gca Ala	gct Ala	ctc Leu 20	cag Gln	gaa Glu	ttt Phe	tat Tyr	gct Ala 25	gag G1u	caa G1n	aag Lys	caa G1n	caa Gln 30	att Ile	gag Glu	96
cca Pro	ggc Gly	gag Glu 35	gat Asp	gat Asp	aaa Lys	tat Tyr	aac Asn 40	att Ile	gga Gly	ata Ile	ata Ile	gaa Glu 45	gag Glu	aat Asn	tgg Trp	144
											gct Ala 60					192
caq	aaa	aca	att.	aca	act.	at.a	aga	gaa	aat	aac	ana	atc	aca	tat	ata	240

G1n 65	Glu	Ala	Ile	Ala	A1a 70	Val	Gly	Glu	Gly	Gly 75	Arg	Пe	Ala	Cys	Val 80		
									aga Arg 90								288
									aaa Lys						gga [.] Gly		336
									aat Asn							,	384
									gta Val							•	432
									tcg Ser							4	480
									ggt Gly 170							í	528
									tgc Cys								576
						Glu			tgt Cys							ć	524
Gly	ctg Leu 210					tga *										6	545

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<211> 214

<212> PRT

<213> Homo sapiens

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 Pro Gly Glu Asp Asp Lys Tyr Asn Ile Gly Ile Ile Glu Glu Asn Trp
                                                 45
 Gln Leu Ser Gln Phe Trp Tyr Ser Gln Glu Thr Ala Leu Gln Leu Ala
 Gin Glu Ala Ile Ala Ala Val Gly Glu Gly Gly Arg Ile Ala Cys Val
 Ser Ala Pro Ser Val Tyr Gln Lys Leu Arg Glu Leu Cys Arg Glu Asn
                 85
                                     90
 Phe Ser Ile Tyr Ile Phe Glu Tyr Asp Lys Arg Phe Ala Met Tyr Gly
                                 105
Glu Glu Phe Ile Phe Tyr Asp Tyr Asn Asn Pro Leu Asp Leu Pro Glu
                             120
Arg Ile Ala Ala His Ser Phe Asp Ile Val Ile Ala Asp Pro Pro Tyr
Leu Ser Glu Glu Cys Leu Arg Lys Thr Ser Glu Thr Val Lys Tyr Leu
                    150
                                         155
Thr Arg Gly Lys Ile Leu Leu Cys Thr Gly Ala Ile Met Glu Glu Gln
                                    170
Ala Ala Glu Leu Leu Gly Val Lys Met Cys Thr Phe Val Pro Arg His
                                185
Thr Arg Asn Leu Ala Asn Glu Phe Arg Cys Tyr Val Asn Tyr Asp Ser
        195
                            200
                                                 205
Gly Leu Asp Cys Gly Ile
    210
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      <221> CDS
      <222> (1)...(264)
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Met Lys Ser Ser Thr Leu Leu Thr Ile Leu Val Leu Gln Ala Leu Leu
                                     10
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gto Val	tct Ser	acg Thr	gcc Ala 20	gtg Val	ccc Pro	aaa Lys	gga Gly	cct Pro 25	Ala	ggc Gly	ccg Pro	aag Lys	aag Lys 30	Gln	tgc Cys	96
tgg Trp	tgc Cys	ggc Gly 35	gag Glu	tgc Cys	acc Thr	agc Ser	tgg Trp 40	tcg Ser	ggc Gly	gtg Val	tgg Trp	acc Thr 45	tgc Cys	gac Asp	gac Asp	144
		acc Thr														192
acg Thr 65	gac Asp	aag Lys	ggc Gly	gcc Ala	acc Thr 70	aag Lys	tac Tyr	aga Arg	tgc Cys	cgc Arg 75	gac Asp	ttc Phe	ctc Leu	ccc Pro	gaa Glu 80	240
		ggc Gly					tag *									264
	<2 <2	210> 211> 212> 213>	87 PRT	sap	iens	į										
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Met 1		Ser		Thr 5	Leu	Leu	Thr	Пe	Leu 10	Val	Leu	Gln	Ala	Leu 15	Leu	
Val	Ser	Thr	Ala 20	Val	Pro	Lys		Pro 25	Ala	Gly	Pro	Lys	Lys 30		Cys	
Trp	Cys	Gly 35	Glu	Cys	Thr				Gly	Val	Trp	Thr 45		Asp	Asp	
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Leu Leu Thr Lys Cys Ala Ala Thr Cys Lys Asn Cys Val Pro Val Ser 50 60

Thr Asp Lys Gly Ala Thr Lys Tyr Arg Cys Arg Asp Phe Leu Pro Glu 65 70 75 80

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Asn Cys Gly Cys Lys Ile His 85

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										Ala		Ser			Tyr	4	18
gtg Val	gaa Glu	tct Ser	atc Ile 20	Cys	tcg Ser	aat Asn	aat Asn	ttt Phe 25	gac Asp	agt Ser	ttc Phe	cta Leu	cat His 30	gaa Glu	act Thr	9	96
cat His	gaa Glu	aac Asn 35	aaa Lys	tac Tyr	gga Gly	aaa Lys	gga Gly 40	att Ile	tac Tyr	ttt Phe	gca Ala	aaa Lys 45	gat Asp	gcc Ala	atc Ile	14	4
tat Tyr	tcc Ser 50	cac His	aaa Lys	aat Asn	tgc Cys	ccg Pro 55	tat Tyr	gat Asp	gcc Ala	aaa Lys	aac Asn 60	gtc Val	gtt Val	atg Met	ttt Phe	19	2
gta Val 65	gcc Ala	caa G1n	gtt Val	ctg Leu	gtt Val 70	gga Gly	aag Lys	ttt Phe	act Thr	gaa Glu 75	gga Gly	aat Asn	ata Ile	acg Thr	tac Tyr 80	24	0
acg Thr	agc Ser	cct Pro	cct Pro	cca Pro 85	cag Gln	ttc Phe	gac Asp	agc Ser	tgt Cys 90	gtg Val	gat Asp	acc Thr	aga Arg	tcg Ser 95	aat Asn	28	8
ccc Pro	tcc Ser	gtt Val	ttt Phe 100	gtc Val	atc Ile	ttt Phe	cag G1n	aaa Lys 105	gat Asp	cag Gln	gtt Val	tac Tyr	cca Pro 110	caa G1n	tat Tyr	336	5
gtg Val												agt Ser 125	tag *			378	3

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<211> 125

<212> PRT

<213> Homo sapiens

	<	400>	110													
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Val	Glu	Ser	Ile 20	Cys	Ser	Asn	Asn	Phe 25	Asp	Ser	Phe	Leu	His 30		Thr	
His	Glu	Asn 35	Lys	Tyr	Gly	Lys	G1y 40	He	Tyr	Phe	Ala	Lys 45		Ala	Ile	
Tyr	Ser 50	His	Lys	Asn	Cys	Pro 55	Tyr	Asp	Ala	Lys	Asn 60	Val	Val	Met	Phe	
Va1 65	Ala	Gln	Val	Leu	Va1 70	Gly	Lys	Phe	Thr	G1u 75	Gly	Asn	Ile	Thr	Tyr 80	
Thr	Ser	Pro	Pro	Pro 85	Gln	Phe	Asp	Ser	Cys 90	۷a٦	Asp	Thr	Arg	Ser 95	Asn	
Pro	Ser	Val	Phe 100	Val	Ile	Phe	Gln	Lys 105	Asp	Gln	Val	Tyr	Pro 110	G1n	Tyr	
Val	Ile	G1u 115	Tyr	Thr	Glu	Asp	Lys 120	Ala	Cys	Va1	Ile	Ser 125				
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											tcg Ser					48
											ttt Phe					96
											aga Arg					144
											gcc Ala 60					192

ctc Leu 65	Leu	cçt Pro	gtc Val	aga Arg	gga Gly 70	Ala	gtt Val	gaa Glu	tgt Cys	tta Leu 75	Phe	gaa Glu	atg Met	ggc Gly	ttt Phe 80	240
					His					Lys					gag Glu	288
								att Ile 105							aga Arg	336
								aaa Lys								384
								aca Thr								432
tta Leu 145	aac Asn	cag Gln	cac His	aca Thr	agg Arg 150	aac Asn	cgt Arg	caa G1n	ggg Gly	cag Gln 155	tca Ser	tca Ser	gat Asp	cca Pro	cca Pro 160	480
								tca Ser								528
								tat Tyr 185								576
aaa Lys	gcg Ala	ttg Leu 195	gct Ala	tgt Cys	att Ile	ccg Pro	gtc Val 200	caa G1n	gaa Glu	cta Leu	aaa Lys	agg Arg 205	aaa Lys	tca Ser	caa G1n	624
Glu					Ala			ttg Leu								672
				Leu				ctt Leu								720

					Asn					Ser					cag Gln	768
act Thr	agg Arg	tct Ser	aga Arg 260	gat Asp	aga Arg	tca Ser	tta Leu	ctg Leu 265	Pro	agt Ser	gat Asp	gat Asp	gag Glu 270	Leu	aag Lys	816
tgg Trp	ggt Gly	gca Ala 275	Lys	gaa Glu	gtg Val	gaa Glu	gat Asp 280	cat His	tac Tyr	tgt Cys	gat Asp	gcc Ala 285	Cys	cag Gln	ttc Phe	864
												ctt Leu				912
												aca Thr				960
												tac Tyr				1008
gtc Val	tgg Trp	aca Thr	gaa Glu 340	gtc Val	tat Tyr	tct Ser	cct Pro	tct Ser 345	cag Gln	cag Gln	cgg Arg	tgg Trp	ctg Leu 350	cac His	tgt Cys	1056
gat Asp	gca Ala	tgt Cys 355	gaa Glu	gat Asp	gtc Val	tgt Cys	gac Asp 360	aag Lys	cca Pro	ctc Leu	ctt Leu	tat Tyr 365	gaa Glu	ata Ile	gga Gly	1104
tgg Trp	ggc Gly 370	aag Lys	aag Lys	ctt Leu	Ser	tat Tyr 375	gtc Val	ata Ile	gca Ala	ttt Phe	tca Ser 380	aaa Lys	gat Asp	gag Glu	gta Val	1152
gtt Val 385	gat Asp	gtc. Val	act Thr	tgg Trp	cga Arg 390	tat Tyr	tcc Ser	tgc Cys	aaa Lys	cat His 395	gaa Glu	gag Glu	gtg Val	Пe	gcc A1a 400	1200
aga Arg	aga Arg	act Thr	Lys	gtt Val 405	aaa Lys	gaa Glu	gca Ala	Leu	ctt Leu 410	cga Arg	gac Asp	act Thr	Ile	aat Asn 415	ggg Gly	1248

				Arg										Lys	gaa Glu	1296
			agg Arg													1344
			cct Pro													1392
			gcc Ala													1440
			tgt Cys													1488
			gtg Val 500													1536
acc Thr	att Ile	tct Ser 515	gga Gly	tgg Trp	gag Glu	aat Asn	ggc G1y 520	gtg Val	tgg Trp	aaa Lys	atg Met	gaa Glu 525	tct Ser	ata Ile	ttc Phe	1584
			gaa Glu													1632
gga Gly 545	tca Ser	tct Ser	ttt Phe	gct Ala	tat Tyr 550	att Ile	tcc Ser	tgg Trp	aag Lys	ttt Phe 555	gag Glu	tgt Cys	999 Gly	tca Ser	gtt Val 560	1680
			gta Val													1728
cag Gln	act Thr	Gly	aca Thr 580	gta Val	gaa Glu	tgg Trp	Lys	ttg Leu 585	cga Arg	tct Ser	gat Asp	Thr	gca Ala 590	caa G1n	gta Val	1776

Glu Leu Ti			t gct gat ttt r Ala Asp Phe 605	0.0
			c aga gga gat r Arg Gly Asp 620	
	rp Gln His		a agc tta aat n Ser Leu Asn 5	
			c agt gac ctt e Ser Asp Leu	tga 1965 *

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<211> 654

<212> PRT

<213> Homo sapiens

<400> 112

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Ser	Ala	Ser	Thr	Val 165	Ala	Ala	Asp	Ser	Ala 170	He	Leu	Glu	Val	Leu 175	Gln
Ser	Asn	Пe	Gln 180	His	Val	Leu	Val	Tyr 185	Glu	Asn	Pro	Ala	Leu 190	Gln	Glu
Lys	Ala	Leu 195	Ala	Cys	Ile	Pro	Val 200	Gln	Glu	Leu	Lys	Arg 205	Lys	Ser	Gln
Glu	Lys 210	Leu	Ser	Arg	Ala	Arg 215	Lys	Leu	Asp	Lys	Gly 220	Ile	Asn	Пe	Ser
Asp 225	Glu	Asp	Phe	Leu	Leu 230	Leu	Glu	Leu	Leu	His 235	Trp	Phe	Lys		G1u 240
Phe	Phe	His	Trp	Va1 245	Asn	Asn	Val	Leu	Cys 250		Lys	Cys	Gly	G1y 255	Gln
Thr	Arg	Ser	Arg 260	Asp	Arg	Ser	Leu	Leu 265	Pro	Ser	Asp	Asp	G1u 270	Leu	Lys
·		275					280				Asp	285	_		
	290					295					Lys 300				
305				-	310		•			315	Phe			•	320
				325					330		Asp			335	
Val	Trp	Thr	G1u 340	Val	Tyr	Ser	Pro	Ser 345	Gln	Gln	Arg	Trp	Leu 350	His	Cys
		355		•			360				Leu	365			•
Trp	G1y 370	Lys	Lys	Leu	Ser	Tyr 375	Val	Ile	Ala	Phe	Ser 380	Lys	Asp	Glu	Val
Va1 385	Asp	Val	Thr	Trp	Arg 390	Tyr	Ser	Cys	Lys	His 395	Glu	Glu	Val	He	Ala 400
Arg	Arg	Thr	Lys	Val 405	Lys	Glu	Ala	Leu	Leu 410	Arg	Asp	Thr	Ile	Asn 415	Gly
Leu	Asn	Lys	G1n 420	Arg	Gln	Leu	Phe	Leu 425	Ser	Glu	Asn	Arg	Arg 430	Lys	G1u
Leu	Leu	G1n 435	Arg	Ile	Ile	Val	G1u 440	Leu	Val	Glu	Phe	Ile 445	Ser	Pro	Lys
Thr	Pro 450	Lys	Pro	Gly	Glu	Leu 455	Gly	Gly	Arg	He	Ser 460	Gly	Ser	۷a٦	Ala
Trp 465	Arg	Val	Ala	Arg	Gly 470	Glu	Met	Gly	Leu	G1n 475	Arg	Lys	Glu	Thr	Leu 480
Phe	He	Pro	Cys	G1u 485	Asn	Glu	Lys	Пе	Ser 490	Lys	Gln	Leu	Ḥis	Leu 495	Cys
Tyr	Asn	Ile	Val 500	Lys	Asp	Arg	Tyr	Val 505	Arg	Va1	Ser	Asn	Asn 510	Asn	Gln

Thr	He	Ser 515	Gly	Trp	Glu	Asn	G1 <i>y</i> 520	Val	Trp	Lys	Met	G1u 525	Ser	Пe	Phe	
Arg	Lys 530	Val	G1u	Thr	Asp	Trp 535	His	Met	Val	Tyr	Leu 540	Ala	Arg	Lys	Glu	
Gly 545	Ser	Ser	Phe	Ala	Tyr 550		Ser	Trp	Lys	Phe 555		Cys	Gly	Ser	Va1 560	
	Leu	Lys	Val	Asp 565		Ile	Ser	Ile	Arg 570		Ser	Ser	Gln	Thr 57.5		
G1n	Thr	Gly	Thr 580		Glu	Trp	Lys	Leu 585		Ser	Asp	Thr	Ala 590		Val	
Glu	Leu	Thr 595		Asp	Asn	Ser	Leu 600		Ser	Tyr	Ala	Asp 605		Ser	Gly	
Ala	Thr 610	Glu	Val	Пe	Leu	G1u 615	Ala	Glu	Leu	Ser	Arg 620		Asp	Gly	Asp	
Val 625	Ala	Trp	GIn	His	Thr 630	Gln	Leu	Phe	Arg	G1n 635		Leu	Asn	Asp	His 640	
Glu	Glu	Asn	Cys	Leu 645	Glu	Ile	Ile	Ile	Lys 650	Phe	Ser	Asp	Leu			
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			(1)	(5	585)											
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	gaa Glu															96
	cct Pro															144
	gga Gly 50															192

				atg Met								240
				gct Ala	 -	-		_		-	,	288
				atg Met								336
				aca Thr								384
				act Thr 135								432
				gac Asp								480
				tat Tyr								528
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ggc Gly	ttc Phe	taa *			•							585

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<211> 194

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<400> 114

WO 01/29221 PCT/US00/29052

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Ser Glu Ser Ser Asn Trp Gly Cys Tyr Gly Asn Ile Gln Ser Leu Asp
Thr Pro Gly Ala Ser Cys Gly Ile Gly Arg Arg His Gly Leu Asn Tyr
                            40
Cys Gly Val Arg Ala Ser Glu Arg Leu Ala Glu Ile Asp Met Pro Tyr
Leu Leu Lys Tyr Gln Pro Met Met Gln Thr Ile Gly Gln Lys Tyr Cys
                     70
                                         75
Met Asp Pro Ala Val Ile Ala Gly Val Leu Ser Arg Lys Ser Pro Gly
                85
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Asp Lys Ile Leu Val Asn Met Gly Asp Arg Thr Ser Met Val Gln Asp
                                 105
Pro Gly Ser Gln Ala Pro Thr Ser Trp Ile Ser Glu Ser Gln Val Ser
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Gln Thr Thr Glu Val Leu Thr Thr Arg Ile Lys Glu Ile Gln Arg Arg
                        135
                                             140
Phe Pro Thr Trp Thr Pro Asp Gln Tyr Leu Arg Gly Gly Leu Cys Ala
                    150
                                         155
                                                             160
Tyr Ser Gly Gly Ala Gly Tyr Val Arg Ser Ser Gln Asp Leu Ser Cys
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Asp Phe Cys Asn Asp Val Leu Ala Arg Ala Lys Tyr Leu Lys Arg His
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Gly Phe
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Met Leu Val Val Glu Val Ala Asn Gly Arg Ser Leu Val Trp Gly Ala
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gag Glu	gcg Ala	gtg Val	cag Gln 20	gcc Ala	ctc Leu	cgg Arg	gag Glu	cgc Arg 25	ctg Leu	ggt Gly	gtg Val	999 Gly	ggc Gly 30	Arg	acg Thr	96
			Leu								tcg Ser				ctc Leu	144
											ttg Leu 60					192
											tct Ser					240
											gag Glu					288
											cgt Arg					336
										-	aag Lys				_	384
											ggc Gly 140					432
gcc Ala 145	aaa Lys	gag Glu	gat Asp	gag Glu	acc Thr 150	agt Ser	gat Asp	ggc Gly	cag Gln	gct Ala 155	tcg Ser	gga Gly	gag Glu	cag G1n	gag Glu 160	480
			Pro								tca Ser					528
		Pro					Leu				gcc Ala					576

								gtc Val				624
								cgc Arg 220				672
								gcg Ala				720
								ctc Leu				768
								acc Thr				816
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	-	-	ctg Leu	-	tga *						!	933

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Val	Gly	A1a 35	Leu	Pro	Arg	Gly	Pro 40	Arg	Gln	Asn	Ser	Arg 45	Leu	Gly	Leu
	50					55					Leu 60				
65					70					75	Ser				80
				85					90		GTu			95	
			100					105			Arg		110		
		115					120				Lys	125			
	130					135					Gly 140				
145					150					155	Ser				160
				165					170		Ser		,	175	
			180	-				185			Ala		190	_	
		195					200				Val	205		-	·
	210					215					Arg 220				
225					230					235	Ala				240
				245					250		Leu			255	
			260					265			Thr		270		
		275					280				Val	285			
	Leu 290	Cys	Ser	Pro	Gln	Pro 295	Asp	Gly	Lys	Val	Va1 300	Tyr	Thr	Ser	Leu
Gln 305	Trp	Ala	Ser	Leu	G1n 310										

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		_	_			gtg Val	_	-	-	_		_		96	
		-				cta Leu			_	-			_	144	
-	-	-				ttg Leu 55		-			_	-		192	
						ccc Pro								240	
				_		tgg Trp		-						288	
						gac Asp								336	
						ctg Leu								384	
						cac His 135								432	

cac His 145	Ile	cac His	tca Ser	ctc Leu	ctg Leu 150	Leu	tat Tyr	gct Ala	ctg Leu	ttc Phe 155	Gly	999 Gly	tgt Cys	gtt Val	agt Ser 160	480
atc Ile	tcc Ser	cta Leu	gag Glu	gtg Val 165	atc Ile	ttc Phe	cgg Arg	gac Asp	cac His 170	att Ile	gtg Val	ctg Leu	gaa Glu	ctt Leu 175	ttc Phe	528
cga Arg	acc Thr	agt Ser	ctc Leu 180	atc Ile	att Ile	ctt Leu	cag Gln	gga Gly 185	acc Thr	tgg Trp	ttc Phe	tgg Trp	cag 61n 190	att Ile	999 Gly	576
ttt Phe	gtg Val	ctg Leu 195	ttc Phe	cca Pro	cct Pro	ttt Phe	gga Gly 200	aca Thr	ccc Pro	gaa Glu	tgg Trp	gac Asp 205	cag G1n	aag Lys	gat Asp	624
gat Asp	gcc Ala 210	aac Asn	ctc Leu	atg Met	ttc Phe	atc Ile 215	acc Thr	atg Met	tgc Cys	ttc Phe	tgc Cys 220	tgg Trp	cac His	tac Tyr	ctg Leu	672
gct Ala 225	gcc Ala	ctc Leu	agc Ser	att Ile	gtg Val 230	gcc Ala	gtc Val	aac Asn	tat Tyr	tct Ser 235	ctt Leu	gtt Val	tac Tyr	tgc Cys	ctt Leu 240	720
ttg Leu	act Thr	cgg Arg	atg Met	aag Lys 245	aga Arg	cac His	gga Gly	agg Arg	gga Gly 250	gaa Glu	atc Ile	att Ile	Gly	att Ile 255	cag G1n	768
aag Lys	ctg Leu	aat Asn	tca Ser 260	gat Asp	gac Asp	act Thr	Tyr	cag G1n 265	acc Thr	gcc Ala	ctc Leu	Leu	agt Ser 270	ggc Gly	tca Ser	816
gat Asp	Glu	-	tga *													828
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                             40
Glu Ala Ala Ile Arg Thr Leu Phe Ser Val Thr Gly Ile Leu Ala Glu
                        55
Gln Phe Val Pro Asp Gly Pro His Leu His Leu Tyr His Glu Asn His
                    70
                                         75
Trp Ile Lys Leu Met Asn Trp Gln His Ser Thr Met Tyr Leu Phe Phe
                                     90
Ala Val Ser Gly Ile Val Asp Met Leu Thr Tyr Leu Val Ser His Val
                                105
Pro Leu Gly Val Asp Arg Leu Val Met Ala Val Ala Val Phe Met Glu
                            120
Gly Phe Leu Phe Tyr Tyr His Val His Asn Arg Pro Pro Leu Asp Gln
                        135
                                            140
His Ile His Ser Leu Leu Leu Tyr Ala Leu Phe Gly Gly Cys Val Ser
                    150
                                        155
Ile Ser Leu Glu Val Ile Phe Arg Asp His Ile Val Leu Glu Leu Phe
                                    170
Arg Thr Ser Leu Ile Ile Leu Gln Gly Thr Trp Phe Trp Gln Ile Gly
                                185
Phe Val Leu Phe Pro Pro Phe Gly Thr Pro Glu Trp Asp Gln Lys Asp
                            200
Asp Ala Asn Leu Met Phe Ile Thr Met Cys Phe Cys Trp His Tyr Leu
                        215
                                            220
Ala Ala Leu Ser Ile Val Ala Val Asn Tyr Ser Leu Val Tyr Cys Leu
                    230
                                        235
Leu Thr Arg Met Lys Arg His Gly Arg Gly Glu Ile Ile Gly Ile Gln
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Lys Leu Asn Ser Asp Asp Thr Tyr Gln Thr Ala Leu Leu Ser Gly Ser
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				Gly					Leu					Pro	acg Thr	ğ	96
			Cys										Asp		acc Thr	14	4
												Ala			aag Lys	19	2
cgg Arg 65	agg Arg	cgc Arg	ctg Leu	ggg Gly	ttc Phe 70	ttg Leu	gcc Ala	acc Thr	gcc Ala	tgg Trp 75	ctc Leu	acc Thr	ttc Phe	tac Tyr	gac Asp 80	24	0
												gcc Ala				28	8
ttt Phe	tat Tyr	atg Met	gaa Glu 100	aaa Lys	gga Gly	aca Thr	cac His	aga Arg 105	ggt Gly	tta Leu	tat Tyr	aaa Lys	agt Ser 110	att Ile	cag Gln	33	6
												gag Glu 125				384	4
Cys .	tta Leu 130	att Ile	gga Gly	att Ile	gta Val	cct Pro 135	act Thr	tct Ser	gtg Val	Ile	gtg Val 140	act Thr	999 Gly	gtc Val	caa G1n	432	2
				He					Leu			cac His				480)
ca i	atc Ile	cag G1n	aat Asn	gaa G1u	gag Glu	agt Ser	gtg Val	gtg Val	ctt Leu	ttt Phe	ctg Leu	gtc Val	gcg Ala	tgg Trp	act Thr	528	}

				165					170					175		
									tac Tyr						•	576
									aga Arg							624
tta Leu	tat Tyr 210	cct Pro	gtt Val	gga Gly	gtt Val	gct Ala 215	ggt Gly	gaa Glu	ctt Leu	ctt Leu	aca Thr 220	ata Ile	tac Tyr	gct Ala	gcc Ala	672
									ttt Phe							720
									tat Tyr 250							768
									ctc Leu							816
						His			gtg Val							864
taa *																867

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<211> 288

<212> PRT

<213> Homo sapiens

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	atc Ile														atc Ile	96
	acc Thr															144
	cgc Arg 50								_	tag *						177
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Mot		100>		Dho	۸cn	Acn	Cvc	Lou	Tun	41 a	Lou	Cua	Val	V-1	۸	
1	Ala			5					10					15	•	
Ihr	Ile	Lys	Arg 20	Ser	Ser	GIn	Ihr	G I y 25	Glu	Trp	GIn	Asn	11e 30	Ala	He	
Met	Thr	G1u 35	Glu	Pro	Glu	Leu	Ser 40	Pro	Ala	Tyr	Leu	Ile 45	Ser	Glu	Ala	
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1				5					10					15	,	
				Cys					His					Gln	aac Asn	96
			Gln			999 Gly		Thr								. 144
999 Gly	ccc Pro 50	Arg	gtt Val	ttc Phe	cag Gln	tac Tyr 55	gga Gly	gtc Val	aaa Lys	gtt Val	gta Val 60	ctt Leu	cag Gln	gct Ala	atg Met	192
						atg Met										240
						ctg Leu										288
						aag Lys										336
						gtg Val										384
Leu						aag Lys 135										432
ctg Leu 145	tgt Cys	gtt Val	acc Thr	aat Asn	gct Ala 150	atg Met	cga Arg	gaa Glu	gac Asp	ctg Leu 155	gcg Ala	gat Asp	aac Asn	tgg Trp	cac His 160	480
			Val			tac Tyr										528
						cac His										576

			180					185	i				190)		
cac His	tct Ser	ccg Pro 195	Phe	agg Arg	gcc Ala	cgc Arg	tca Ser 200	Glu	cct Pro	gag Glu	gac Asp	cca Pro 205	Val	acg Thr	gag Glu	624
		Ala					Asp					Leu			cgt Arg	672
						Leu			agc Ser		Thr				gag Glu 240	720
					He				gct Ala 250							. 768
									tct Ser							816
									agc Ser							864
									ccc Pro							912
									ctg Leu							960
									aag Lys 330							1008
							Val		ttc Phe							1056
gtg Val	aaa Lys	cat His	gaa Glu	gaa Glu	aat Asn	ggc Gly	ctg Leu	gtc Val	ttt Phe	gag Glu	gac Asp	tca Ser	gag Glu	gaa Glu	ctg Leu	1104

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		Gln					Phe	tca Ser				Asp			gca Ala	1:	152
agc Ser 385																13	158
	< < <	211> 212> 213>		o sa	pien	S-							. •				
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Asn	Arg	I 1e 35	Gln	Пe	Val	Gly	Leu 40	Thr	Glu	Leu	Gln	Ser 45		Ala	Val		
Gly	Pro 50	Arg	Val	Phe	Gln	Tyr 55	Gly	Val	Lys	Val	Val 60		.G1n	Ala	Met		
Tyr 65	Leu	Leu	Trp	Lys	Leu 70	Met	Trp	Arg	Glu	Pro 75	Gly	Ala	Tyr	Ile	Phe 80		
Leu	Gln	Asn	Pro	Pro 85	Gly	Leu	Pro	Ser	Ile 90	Ala	Val	Cys	Trp	Phe 95	Val		
Gly	Cys	Leu	Cys 100	Gly	Ser	Lys	Leu	Val 105	Ile	Asp	Trp	His	Asn 110	Tyr	Gly		
Tyr	Ser	Ile 115	Met	Gly	Leu	Val	His 120	Gly	Pro	Asn	His	Pro 125	Leu	Val	Leu		
	130					135		Phe			140						
Leu 145	Cys	Val	Thr	Asn	Ala 150	Met	Arg	Glu	Asp	Leu 155	Ala	Asp	Asn	Trp	His 160		
Ile	Arg	Ala	Val	Thr 165	Val	Tyr	Asp	Lys	Pro 170	Ala	Ser	Phe	Phe	Lys 175			
Thr	Pro	Leu	Asp 180	Leu	G1n	His	Arg	Leu 185	Phe	Met	Lys	Leu	Gly 190		Met		
His	Ser	Pro 195		Arg	Ala	Arg	Ser 200	Glu	Pro	Glu	Asp	Pro 205		Thr	Glu		
Arg	Ser		Phe	Thr	Glu	Arg		Ala	Gly	Ser	Gly		Val	Thr	Arg		

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Leu 225		Glu	Arg	Pro	Ala 230	Leu		ı Val	Ser	Ser 235	Thr		Trp	Thr	Glu 240	
Asp	Glu	Asp	Phe	Ser 245	Ile		Leu	ı Ala	Ala 250	Leu		Lys	Phe	G1u 255	Gln	
Leu	Thr	Leu	Asp 260	Gly	His	Asn	Leu	Pro 265	Ser		Val	Cys	Va1 270	Πe	Thr	
Gly	Lys	G1y 275	Pro	Leu	Arg	Glu	Tyr 280		Ser	Arg	Leu	Ile 285			Lys	
	290					295					300				Asp	
Tyr 305	Pro	Leu	Leu	Leu	Gly 310	Ser	Ala	Asp	Leu	Gly 315		Cys	Leu	His	Thr 320	
				325					330					335	Gly	
			340					345					350		Leu	
		355				Gly	360					365				
Ala	Ala 370	Gln	Leu	Gln	Met	Leu 375	Phe	Ser	Asn	Phe	Pro 380	Asp	Leu	Arg	Ala	
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ggc (Gly (ggc (Gly (ggc (Gly (ggc (Gly (999 (Gly (ggc (Gly /	gcc q Ala (ggc Gly	ggc Gly	tgc Cvs	999 Gly	gcg Ala	ctg Leu	act Thr	gcc Ala	ggc Glv	96

			20)				25	5				30)		
tgo Cys	tto Phe	cct Pro 35	o Gly	ctg Leu	ggg Gly	gto Val	ago Ser 40	· Arg	cac His	cgg Arg	g cag g Glr	g cag n Gln 45	G1r	cad His	cac His	144
cgg Arg	acg Thr 50	' Val	a cac His	cag Gln	agg Arg	ato Ile 55	Ala	tcc Ser	tgg Trp	cag Gln	aat Asn 60	Leu	gga Gly	agct Ala	gtt Val	192
tat Tyr 65	Cys	ago Ser	act Thr	gtt Val	gtg Val 70	Pro	tct Ser	gat Asp	gat Asp	gtt Val 75	Thr	gtg Val	gtt Val	tat Tyr	caa 61n 80	240
aat Asn	ggg Gly	tta Leu	cct Pro	gtg Val 85	He	tct Ser	gtg Val	agg Arg	cta Leu 90	cca Pro	tcc Ser	cgg Arg	cgt Arg	gaa Glu 95	cgc Arg	288
tgt Cys	cag Gln	ttc Phe	aca Thr 100	ctc Leu	aag Lys	cct Pro	atc Ile	tct Ser 105	gac Asp	tct Ser	gtt Val	ggt Gly	gta Val 110	Phe	.tta Leu	336
cga Arg	caa Gln	ctg Leu 115	caa G1n	gaa Glu	gag Glu	gat Asp	cgg Arg 120	gga Gly	att Ile	gac Asp	aga Arg	gtt Val 125	gct Ala	atc Ile	tat Tyr	384
tca Ser	cca Pro 130	gat Asp	ggt Gly	gtt Val	cgc Arg	gtt Val 135	gct Ala	gct Ala	tca Ser	aca Thr	gga Gly 140	ata Ile	gac Asp	ctc Leu	ctc Leu	432
ctc Leu 145	ctt Leu	gat Asp	gac Asp	ttt Phe	aag Lys 150	ctg Leu	gtc Val	att Ile	Asn	gac Asp 155	tta Leu	aca Thr	tac Tyr	cac His	gta Val 160	480
cga Arg	cca Pro	cca Pro	aaa Lys	aga Arg 165	gac Asp	ctc Leu	tta Leu	agt Ser	cat His 170	gaa Glu	aat Asn	gca Ala	gca Ala	acg Thr 175	ctg Leu	528
aat Asn	gat Asp	gta Val	aag Lys 180	aca Thr	ttg Leu	gtc Val	cag G1n	caa Gln 185	cta Leu	tac Tyr	acc Thr	Thr	ctg Leu 190	tgc Cys	att Ile	576
gag Glu	cag G1n	cac His	cag G1n	tta Leu	aac Asn	aag Lys	gaa Glu	agg Arg	gag Glu	ctt Leu	att Ile	gaa Glu	aga Arg	cta Leu	gag Glu	624

		195	•				200	I				205				
		ı Lys					Pro					cga Arg				672
ago Ser 225	Arg	aaa Lys	gct Ala	gag Glu	aag Lys 230	agg Arg	acc Thr	act Thr	ttg Leu	gtg Val 235	cta Leu	tgg Trp	ggt Gly	ggc Gly	ctt Leu 240	720
												ctt Leu				768
												ttc Phe				816
gga Gly	agt Ser	gcc Ala 275	atg Met	gca Ala	atg Met	tat Tyr	gca Ala 280	tat Tyr	ttt Phe	gta Val	atg Met	aca Thr 285	cgc Arg	cag Gln	gaa Glu	864
												cta Leu				912
aaa Lys 305	gga Gly	gcc Ala	aaa Lys	aag Lys	tca Ser 310	cgt Arg	ttt Phe	gac Asp	cta Leu	gag Glu 315	aaa Lys	tac Tyr	aat Asn	caa Gln	ctc Leu 320	960
aag Lys	gat Asp	gca Ala	He	gct Ala 325	cag Gln	cag Gln	aaa Lys	Trp	acc Thr 330	tta Leu	aga Arg	gac Asp	tga *			1002
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Cys	Phe	Pro 35	Gly	Leu	Gly	Val	Ser 40	Arg	His	Arg	Gln	G1n 45		His	His
Arg	Thr 50	Val	His	Gln	Arg	Ile 55	Ala	Ser	Trp	Gln	Asn 60	Leu	Gly	Ala	۷a۱
Tyr 65	Cys	Ser	Thr	Val	Va1 70	Pro	Ser	Asp	Asp	Va1 75	Thr	Val	Val	Tyr	G1r 80
Asn	Gly	Leu	Pro	Va1 85	Пе	Ser	Val	Arg	Leu 90	Pro	Ser	Arg	Arg	G1u 95	Arg
Cys	G1n	Phe	Thr 100	Leu	Lys	Pro	Ile	Ser 105	Asp	Ser	Val	Gly	Val 110	Phe	Leu
		115	Gln				120					125			_
	130		Gly			135					140		•		
145			Asp		150					155			-		160
			Lys	165	·				170					175	
			Lys 180					185					190	•	
		195	Gln				200					205			
	210		Glu			215					220				
225			Ala		230					235		·	-	-	240
			Ala	245					250		_			255	•
			Trp 260	,				265			•		270		Ü
		275	Met				280					285			
	290		Pro			295	•				300				
305			Lys		310					315			Asn	Gln	Leu 320
Lys	Asp	Ala	Пe	Ala 325	Gln	Gln	Lys	Trp	Thr 330	Leu	Arg	Asp			

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tcc Ser	cag Gln	atg Met	ctt Leu 20	999 Gly	ggc Gly	cta Leu	gga Gly	cag Gln 25	gat Asp	gtt Val	ttg Leu	tta Leu	aat Asn 30	aat Asn	tca Ser	96
						ggc Gly										144
aag Lys	ccc Pro 50	agc Ser	tcc Ser	gtg Val	ttc Phe	aga Arg 55	aat Asn	gga Gly	ttc Phe	tct Ser	ggc Gly 60	att Ile	aag Lys	aag Lys	cct Pro	192
tgg Trp 65	cac His	aga Arg	tgt Cys	cac His	gtc Val 70	tgc Cys	aac Asn	cac His	cac His	ttc Phe 75	cag Gln	ttc Phe	aaa Lys	cag Gln	cac His 80	240
						aca Thr										288
cgg Arg	att Ile	tgt Cys	cgc Arg 100	aag Lys	tcc Ser	tat Tyr	gta Val	cgt Arg 105	cct Pro	ggc Gly	agc Ser	ctg Leu	agc Ser 110	aca Thr	cac His	336
atg	aaa	ctt	cat	cat	ggt	gag	aac	cgt	ctg	aag	aaa	ctc	atg	tgt	tgt	384

Met	Lys	Leu 115	His	His	Gly	Glu	Asn 120	Arg	Leu	Lys	Lys	Leu 125	Met	Cys	Cys	
					gtg Val											432
					agg Arg 150											480
					gac Asp											528
					ttg Leu											576
					cag Gln		-	-	- ·						_	624
					act Thr											672
					gga Gly 230											720
acc Thr	ttc Phe	cca Pro	gga Gly	agc Ser 245	aag Lys	999 Gly	act Thr	cag G]n	gaa G1u 250	gag Glu	ttg Leu	gtg Val	cag Gln	cac His 255	gct Ala	768
		Asp		Lys	agg Arg							Pro				816
	Ser				gaa Glu	Ser					Arg					864
ctc	cac	ctt	cat	cag	aat	ggc	gtg	gaa	atg	ctc	atg	gaa	aat	gaa	gga	912

Leu	His 290		His	Gln	Asn	Gly 295	Val	Glu	ı Met	Leu	Met 300		ı Asn	G]ı	Gly	
ecc Pro 305	Gln	tca Ser	gga Gly	acc Thr	aac Asn 310	aag Lys	cca Pro	agg Arg	gaa Glu	acc Thr 315	Cys	cag Gln	ggc Gly	cct Pro	gag G1u 320	960
tgt Cys	cct Pro	ggc Gly	ctc Leu	cac His 325	Thr	ttt Phe	ctc Leu	ttg Leu	tgg Trp 330	Ser	cat His	tca Ser	ggc Gly	ttt Phe 335	aac Asn	1008
tgc Cys	ctg Leu	ctt Leu	tgt Cys 340	gca Ala	gag Glu	atg Met	ctg Leu	gga Gly 345	Arg	aaa Lys	gag G1ù	gac Asp	ctc Leu 350	ctc Leu	cac His	1056
cac His	tgg Trp	aag Lys 355	cac His	cag Gln	cat His	aac Asn	tgt Cys 360	gag Glu	gac Asp	cct Pro	tcc Ser	aaa Lys 365	ctg Leu	tgg Trp	gct Ala	1104
att Ile	tta Leu 370	aat Asn	acg Thr	gtc Val	tcc Ser	aac Asn 375	cag G1n	gga Gly	gtg Val	atc Ile	gaa G1u 380	ctt Leu	tcc Ser	agt Ser	gaa Glu	1152
	gag Glu		tga *													1164
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Met 1				Thr 5	Leu .	Ala:	Ser	Leu	Ala 10	Ser	Pro	Thr	Thr	Leu 15	G1n	
_	Gln				Gly	Leu (Val	Leu	Leu			Ser	
Leu	Thr		20 Lys	Tyr	Leu (Gly (25 Lys	G1n	Asp	Asn	Ser	30 Ser	Ser	Pro	

		35					40					45			
Lys	Pro 50	s Se	r Sei	r Va	1 Phe	Arg 55	g Ası	n Gly	y Phe	e Sei	r Glչ 60	y Ile	e Lys	S Lys	s Pro
Trp 65	His	s Ar	g Cys	s His	s Val 70		S Asr	n His	s His	s Phe 75		n Phe	e Lys	G]r	n His 80
Leu	Arç	g Ası	p His	Met 85	. Asn	Thr	His	Thr	^ Asr 90	n Arg	g Arg	g Pro) Tyr	Ser 95	Cys
Arg	Πe	e Cys	s Arg 100	j Lys)	Ser	Tyr	' Val	Arg 105		Gly	/ Ser	Lei	Ser	Thr	His
		115	5		Gly		120)				125	Met	Cys	
Glu	Phe 130	Cys	s Ala	Lys	Val	Phe 135	G1y	His	Ile	Arg	Val 140	Tyr	Phe	G1y	His
145					Arg 150					155)				160
				165					170					175	Arg
			180		Leu			185					190		
		195	,		G1n		200					205			-
	210				Thr	215					220				
225					Gly 230					235					240
				245	Lys				250					255	
			260		Arg			265					270		
		275			Glu		280					285			
	290					295					300				-
305					Asn 310					315					320
				325	Thr				330					335	
			340		G1u i			345					350	Leu	
		355			His ,		360					365			
,	370		Thr	Val	Ser /	Asn 375	Gln	G1y	Val		G1u 380	Leu	Ser	Ser	Glu
\la (Glu	Lys													

385

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agg Arg	cct Pro	tat Tyr 115	· Gly	gta Val	a caa I G1r	agg Arg	aca Thr 120	Lys	att Ile	gct Ala	caa Gli	a gat n Asp 129) []e	t gaa e Glu	a agg ı Arg		384
cta Leu	ata Ile 130	His	cag Glr	agt Ser	gat Asp	ato Ile 135	: Ile	gat Asp	cgt Arg	gtg Val	gta Val 140	l Tyr	gac Sac	ttg Lei	gat Asp		432
aac Asn 145	cca Pro	aat Asn	tac Tyr	acc Thr	att Ile 150	Pro	gaa G1u	gag Glu	gga Gly	gat Asp 155	He	ttg Lei	aaa Lys	ttt Phe	aac Asn 160		480
tcc Ser	aaa Lys	ttt Phe	gag Glu	tct Ser 165	Gly	aat Asn	ctg Leu	cgc Arg	ana Xaa 170	Val	att	caa Gln	att Ile	aga Arg 175	aaa Lys		528
aat Asn	gaa Glu	tat Tyr	gat Asp 180	Leu	att Ile	ctg Leu	aac Asn	tca Ser 185	gac Asp	ata Ile	aac Asn	agc Ser	aat Asn 190	His	tat Tyr	!	576
cat His	cag Gln	tgg Trp 195	ttt Phe	tac Tyr	ttt Phe	gaa Glu	gtc Val 200	agt Ser	gga Gly	atg Met	cga Arg	cca Pro 205	ggt Gly	gtt Val	gct Ala	(524
Tyr	agg Arg 210	ttt Phe	aac Asn	atc Ile	att Ile	aac Asn 215	tgt Cys	gaa Glu	aag Lys	tcc Ser	aac Asn 220	agt Ser	cag Gln	ttt Phe	aat Asn	•	572
tat Tyr 225	ggt Gly	atg Met	caa G1n	cca Pro	ctc Leu 230	atg Met	tat Tyr	tcg Ser	gtt Val	cag G1n 235	gaa Glu	gca Ala	tta Leu	aat Asn	gcc Ala 240	7	720
aga Arg	cca Pro	tgg Trp	tgg Trp	att Ile 245	cgt Arg	atg Met	999 Gly	act Thr	gac Asp 250	att Ile	tgt Cys	tac Tyr	tat Tyr	aaa Lys 255	aat Asn	7	'68
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ac yr	Tyr	aca Thr 275	att Ile	aca Thr	ttt Phe	Thr	gtc Val 280	aat Asn	ttt Phe	cca Pro	cat His	aaa Lys 285	gat Asp	gat Asp	gtt Val	8	64

tgo Cys	tac Tyr 290	· Phe	t gct e Ala	tat Tyr	cac His	tat Tyr 295	Pro	a tat) Tyr	acq Thi	g tai ^ Tyr	t toa Ser 300	Thr	t tta Lei	a caq ıGlr	atg Met	912
	Lei					Ser					Glr				ttt Phe 320	960
cgg Arg	aaa Lys	gat Asp	gtg Val	tta Leu 325	Cys	gaa Glu	acc Thr	ctg Leu	tct Ser 330	· Gly	aac Asn	ago Ser	tgc Cys	Pro 335	Leu	1008
gtg Val	act Thr	ata Ile	aca Thr 340	gca Ala	atg Met	cca Pro	gag Glu	tct Ser 345	Asn	tat Tyr	tat Tyr	gaa Glu	cat His 350	Пe	tgc Cys	1056
cat His	ttc Phe	aga Arg 355	Asn	cgc Arg	cct Pro	tac Tyr	gtt Val 360	ttc Phe	ttg Leu	tct Ser	gct Ala	cgg Arg 365	Val	cat His	cct Pro	1104
gga Gly	gaa G1u 370	act Thr	aat Asn	gca Ala	agt Ser	tgg Trp 375	gtt Val	atg Met	aaa Lys	gga Gly	acg Thr 380	ttg Leu	gaa Glu	tat Tyr	ctc Leu	1152
atg Met 385	agc Ser	aat Asn	aac Asn	ccc Pro	act Thr 390	gct Ala	cag G1n	agc Ser	tta Leu	cga Arg 395	gaa Glu	tct Ser	tat Tyr	att Ile	ttt Phe 400	1200
aaa Lys	att Ile	gtc Val	cct Pro	atg Met 405	tta Leu	aat Asn	cca Pro	gat Asp	ggt Gly 410	gtc Val	atc Ile	aat Asn	gga Gly	aat Asn 415	cat His	1248
cgc Arg	tgt Cys	tct Ser	tta Leu 420	agt Ser	gga Gly	gag Glu	gat Asp	ttg Leu 425	aat Asn	agg Arg	cag Gln	tgg Trp	caa Gln 430	agt Ser	cca Pro	1296
agt Ser	Pro	gat Asp 435	tta Leu	cat His	cct Pro	Thr	att Ile 440	tac Tyr	cat His	gct Ala	aag Lys	ggg Gly 445	ctg Leu	ttg Leu	caa Gln	1344
Tyr	ttg Leu 450	gct Ala	gca Ala	gtg Val	Lys	cgt Arg 455	tta Leu	ccc Pro	ttg Leu	Val	tat Tyr 460	tgt Cys	gat Asp	tat Tyr	cat His	1392

ggc Gly 465	His	t too S Ser	cga Arq	a aaq g Lys	aaq Lys 470	s Asr	gta Val	a ttt I Phe	t atq e Met	g ta t Tyi 47!	r Gly	t tgo / Cy:	c ago S Sei	c ato	c aaa e Lys 480	1440
gag Glu	aca Thr	a gtg 'Val	tgg Trp	cat His 485	Thr	aat Asn	gat Asp	aat Asr	gca 1 Ala 490	Thr	t tca Ser	tgi Cys	gat S Asp	gt: Va ⁻ 495	t gtg Val	1488
gag Glu	gat Asp	acg Thr	gga Gly 500	Tyr	: agg · Arg	aca Thr	ttg Leu	cct Pro 505	Lys	ıata ∶Il∈	a ctg e Leu	ago Ser	cat His 510	Πe	gcc Ala	1536
cca Pro	gca Ala	ttt Phe 515	Cys	atg Met	agc Ser	agc Ser	tgt Cys 520	Ser	ttc Phe	gta Val	gtg Val	gaa G1u 525	Lys	tct Ser	aaa Lys	1584
gaa Glu	tcc Ser 530	aca Thr	gca Ala	cgt Arg	gtt Val	gta Val 535	gtt Val	tgg Trp	agg Arg	gaa Glu	ata Ile 540	Gly	gta Val	caa G1n	aga Arg	1632
agt Ser 545	tat Tyr	acc Thr	atg Met	gag Glu	agt Ser 550	act Thr	tta Leu	tgt Cys	ggc Gly	tgt Cys 555	gat Asp	cag G1n	gga Gly	aaa Lys	tac Tyr 560	1680
aag Lys	ggt Gly	tta Leu	cag Gln	att Ile 565	ggt Gly	acc Thr	cga Arg	gaa Glú	ctg Leu 570	gaa Glu	gag Glu	atg Met	gga Gly	gca Ala 575	aaa Lys	1728
ttt Phe	tgt Cys	gtt Val	ggt Gly 580	ctt Leu	tta Leu	cgt Arg	ttg Leu	aaa Lys 585	aga Arg	ctg Leu	acc Thr	tct Ser	cca Pro 590	ttg Leu	gag Glu	1776
tat Tyr	aat Asn	ctg Leu 595	cct Pro	tcc Ser	agc Ser	Leu	ctt Leu 600	gac Asp	ttt Phe	gaa Glu	aat Asn	gat. Asp 605	tta Leu	att Ile	gaa Glu	1824
Ser	agc Ser 610	tgc Cys	aaa Lys	gta Val	Thr	agc Ser 615	cct Pro	acc Thr	act Thr	tat Tyr	gtc Val 620	ttg Leu	gat Asp	gaa G1u	gat Asp	1872
gaa Glu 625	cct Pro	cga Arg	ttc Phe	Leu	gaa Glu 630	gaa Glu	gtt Val	gat Asp	Tyr	agt Ser 635	gca Ala	gaa Glu	agt Ser	aat Asn	gat Asp 640	1920

gag tta gat att gag ttg gct gaa aat gta gga gat tat gaa cct tct 1968 Glu Leu Asp Ile Glu Leu Ala Glu Asn Val Gly Asp Tyr Glu Pro Ser 645 650 655 gct caa gaa gaa gta ctt tct gac tct gaa tta tca aga aca tac cta 2016 Ala Gln Glu Val Leu Ser Asp Ser Glu Leu Ser Arg Thr Tyr Leu 660 670 cct tga 2022 Pro * <210> 130 <211> 673 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(673) <223> Xaa = Any Amino Acid <400> 130 Met Lys Lys Asp Cys Ser Leu Pro Leu Thr Val Leu Thr Cys Ala Lys Ala Cys Pro His Met Ala Thr Cys Gly Asn Val Leu Phe Glu Gly Arg Thr Val Gln Leu Gly Lys Leu Cys Cys Thr Gly Val Glu Thr Glu Asp 40 45 Asp Glu Asp Thr Glu Ser Asn Ser Ser Val Glu Gln Ala Ser Val Glu Val Pro Asp Gly Pro Thr Leu His Asp Pro Asp Leu Tyr Ile Glu Ile 75 Val Lys Asn Thr Lys Ser Val Pro Glu Tyr Ser Glu Val Ala Tyr Pro 85 90 Asp Tyr Phe Gly His Ile Pro Pro Pro Phe Lys Glu Pro Ile Leu Glu 105 Arg Pro Tyr Gly Val Gln Arg Thr Lys Ile Ala Gln Asp Ile Glu Arg 115 120 125 Leu Ile His Gln Ser Asp Ile Ile Asp Arg Val Val Tyr Asp Leu Asp 135 140 Asn Pro Asn Tyr Thr Ile Pro Glu Glu Gly Asp Ile Leu Lys Phe Asn 150 155

Ser	Lys	Phe	e Glu	Ser 165		Asn	Leu	Arg	Xaa 170		Ile	Gln	Ile	Arg 175	Lys
Asn	Glu	Tyr	Asp 180		Ile	Leu	Asn	Ser 185		Ile	Asn	Ser	Asn 190		Tyr
His	Gln	Trp 195		Tyr	Phe	Glu	Val 200		Gly	Met	Arg	Pro 205		Val	Ala
Tyr	Arg 210		Asn	Ile	Ile	Asn 215		Glu	Lys	Ser	Asn 220	Ser	Gln	Phe	Asn
225					230					235	Glu				240
				245					250		Cys			255	
			260					265			G1n		270	_	
		275					280				His	285		•	
	290					295					Ser 300				
305					310					315	Gln			,	320
				325					330		Asn			335	
			340					345			Tyr		350		•
		355					360				Ala	365			
	370					375					Thr 380			•	
385					390				•	395	Glu				400
				405					410		Ile		-	415	
			420					425			Gln	·	430		
		435					440					445			
	450					455					Tyr 460				
G1y 465	His	Ser	Arg		Lys 470	Asn	Val	Phe		Tyr 475	Gly	Cys	Ser		Lys 480
				485					490		Ser	•	•	495	
Glu	Asp		Gly 500	Tyr	Arg	Thr		Pro 505	Lys	Ile	Leu		His 510	Пe	Ala

Pro	Ala	Phe 515	Cys	Met	Ser	` Ser	Cys 520		· Phe	e Va	l Val	Glu 525		s Ser	^ Lys	
Glu	Ser 530	Thr	Ala	Arg	Va1	Val 535	Val		Arç	g Glu	Ile 540	Gly		Glr	n Arg	
Ser 545	Tyr	Thr	Met	Glu	Ser 550	Thr		Cys	Gly	Cys 555	s Asp	Gln	Gly	/ Lys	Tyr 560	
		Leu	Gln	I1e 565	Gly		Arg	Glu	Leu 570	Glu		Met	Gly	A1a 575	Lys	
Phe	Cys	Val	Gly 580	Leu		Arg	Leu	Lys 585	Arg		ı Thr	Ser	Pro 590	Leu	, Glu	
Tyr	Asn	Leu 595	Pro	Ser	Ser	Leu	Leu 600	Asp		Glu	ı Asn	Asp 605			Glu	
Ser	Ser 610	Cys	Lys	Val	Thr	Ser 615	Pro	Thr	Thr	Tyr	Val 620	Leu	Asp	Glu	Asp	
G1u 625	Pro	Arg	Phe	Leu	G1u 630	Glu	Val	Asp	Tyr	Ser 635		Glu	Ser	Asn	Asp 640	
				645					650					655	Ser	
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gat Asp	tat Tyr :	tct Ser	ttg Leu 20	gcc Ala	gtt Val	gct Ala	ttc Phe	cta Leu 25	act Thr	ata Ile	tca Ser	aca Thr	aca Thr 30	ctg Leu	gga Gly	96
ggc i Gly f	ttt Phe (tgc (Cys) S	tct Ser S	tct (Ser (gga Gly I	ttt . Phe :	agc Ser	atc Ile .	aac Asn	cat His	ctg Leu	gat Asp	att Ile	gct Ala	cct Pro	144

		· Ala										Phe			att Ile	192
	Gly	atg Met									Leu					240
		gga Gly														288
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		gct Ala 115						Gly				_				375
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Gly	Phe	Cys 35		Ser	Gly		Ser 40		Asn	His	Leu	Asp 45		Ala	Pro	
Ser	Tyr 50	Ala	Gly	Пе	Leu			Ile	Thr	Asn	Thr 60		Ala	Thr	He	
Pro 65		Met	Val	Gly	Pro 70		Ile	Ala	Lys	Ser 75		Thr	Pro	Asp	Asn 80	
	Val	Gly		Trp 85		Thr	Val	Phe	Tyr 90		Ala	Ala	Ala	Ile 95		
Va]	Phe	Gly			Phe	Phe	Thr	Leu 105		Ala	Lys	Gly	G1u 110		G1n	
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	ttt Phe		Cys					Leu								144
	tac Tyr 50															192
gcc Ala 65	acc Thr	ttc Phe	atg Met	gac Asp	cca Pro 70	999 Gly	att Ile	ttc Phe	cct Pro	cga Arg 75	gct Ala	gag Glu	gag Glu	gat Asp	gag G1u 80	240
	aag Lys															288
aag Lys	ggc Gly	atc Ile	cag Gln 100	gtg Val	cgc Arg	atg Met	aaa Lys	tgg Trp 105	tgt Cys	gcc Ala	acc Thr	tgc Cys	cgc Arg 110	ttt Phe	tac Tyr	336
cgt	ccc	cct	cga	tgt	tcc	cac	tgc	agt	gtc	tgt	gac	aac	tgt	gtg	gag	384

Arg	Pro	Pro 115		Cys	Ser	His	Cys 120		Val	Cys	Asp	Asn 125		Val	Glu	
gaa G1u	ttt Phe 130	Asp	cat His	cac His	tgc Cys	ccc Pro 135	tgg Trp	gtg Val	aat Asn	aac Asn	tgt Cys 140	Пe	ggt Gly	. cgc . Arg	cgg Arg	432
aac Asn 145	Tyr	cgt Arg	tat Tyr	ttt Phe	ttc Phe 150	ctt Leu	ttc Phe	ctc Leu	ctt Leu	tcc Ser 155	Leu	aca Thr	gcc Ala	cac	att Ile 160	480
				ggc Gly 165											Glu	528
				gtc Val												576
				ttc Phe												624
				agg Arg												672
ttc Phe 225	cgg Arg	gga Gly	ggt Gly	gtg Val	aac Asn 230	ccc Pro	ttc Phe	acc Thr	aat Asn	ggc G1y 235	tgc Cys	tgt Cys	aac Asn	aat Asn	gtc Val 240	720
				tgc Cys 245												768
		Glu		aca Thr			Пe									816
	Ser			cag Gln		Thr					Asp					864
gga	gag	ctg	agg	aga	aca	aag	tct	aag	gga	agc	ctg	gag	ata	aca	gag	912

G1y	Glu 290		ı Arg	1 Arg	Thr	Lys 295		Lys	Gly	Ser	Leu 300		ı Ile	thr	· Glu	
	Gln					Glu) Pro				ctg Leu 320	960
										Gly	ttg Leu				Glu	1008
				Leu							aca Thr			Met		1056
aag Lys	tat Tyr	cgg Arg 355	Pro	ggt Gly	tac Tyr	agt Ser	agc Ser 360	agc Ser	agt Ser	acg Thr	tca Ser	gct Ala 365	gcc Ala	atg Met	ccg Pro	1104
cat His	tcc Ser 370	tcc Ser	agc Ser	gcc Ala	aag Lys	ttg Leu 375	agt Ser	cgt Arg	999 Gly	gac Asp	agc Ser 380	ttg Leu	aag Lys	gag Glu	cca Pro	1152
acc Thr 385	tca Ser	att Ile	gca Ala	gag Glu	agc Ser 390	agc Ser	cgt Arg	cac His	ccc Pro	agc Ser 395	tac Tyr	cgc Arg	tca Ser	gag Glu	ccc Pro 400	1200
agc Ser	ttg Leu	gaa Glu	cca Pro	gag G1u 405	agc Ser	ttc Phe	cgt Arg	tct Ser	cct Pro 410	acc Thr	ttt Phe	ggc Gly	aaa Lys	agt Ser 415	ttt Phe	1248
cac His	ttc Phe	gat Asp	cca Pro 420	cta Leu	tcc Ser	agt Ser	Gly	tca Ser 425	cgc Arg	tcc Ser	tcc Ser	agc Ser	ctc Leu 430	aag Lys	tca Ser	1296
ncc Xaa	G1n	ggc Gly 435	aca Thr	ggc Gly	ťtt Phe	Glu	ctg Leu 440	ggc Gly	cag G1n	ttg Leu	caa Gln	tcc Ser 445	att Ile	cgt Arg	tca Ser	1344
Glu	ggc Gly 450	acc Thr	acc Thr	tcc Ser	Thr	tcc Ser 455	tat Tyr	aag Lys	agc Ser	ctg Leu	gcc Ala 460	aac Asn	cag G1n	aca Thr	cgc Arg	1392
aat	gga	agc	cta	tct	tat	gac	agc	ttg	ctc	aca	cct	tca	gac	agc	cct	1440

Asn Gly Ser Leu Ser Tyr Asp Ser Leu Leu Thr Pro Ser Asp Ser Pro 465 470 475 gat ttt gag tca gtg cag gca ggg ctg agc cag acc cac ctt tag 1485 Asp Phe Glu Ser Val Gln Ala Gly Leu Ser Gln Thr His Leu * 485 <210> 134 <211> 494 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(494) <223> Xaa = Any Amino Acid <400> 134 Met Pro Ala Glu Ser Gly Lys Arg Phe Lys Pro Ser Lys Tyr Val Pro Val Ser Ala Ala Ala Ile Phe Leu Val Gly Ala Thr Thr Leu Phe Phe Ala Phe Thr Cys Pro Gly Leu Ser Leu Tyr Val Ser Pro Ala Val Pro 40 45 Ile Tyr Asn Ala Ile Met Phe Leu Phe Val Leu Ala Asn Phe Ser Met Ala Thr Phe Met Asp Pro Gly Ile Phe Pro Arg Ala Glu Glu Asp Glu 75 Asp Lys Glu Asp Asp Phe Arg Ala Pro Leu Tyr Lys Thr Val Glu Ile

85 90 95
Lys Gly Ile Gln Val Arg Met Lys Trp Cys Ala Thr Cys Arg Phe Tyr
100 105 110
Arg Pro Pro Arg Cys Ser His Cys Ser Val Cys Asp Asp Cys Val Glu

Arg Pro Pro Arg Cys Ser His Cys Ser Val Cys Asp Asn Cys Val Glu
115
120
125

Glu Phe Asp His His Cys Pro Trp Val Asn Asn Cys Ile Gly Arg Arg 130 135 140

Asn Tyr Arg Tyr Phe Phe Leu Phe Leu Leu Ser Leu Thr Ala His Ile 145 150 155 160

Met Gly Val Phe Gly Phe Gly Leu Leu Tyr Val Leu Tyr His Ile Glu 165 170 175

Glu Leu Ser Gly Val Arg Thr Ala Val Thr Met Ala Val Met Cys Val 180 185 190 Ala Gly Leu Phe Phe Ile Pro Val Ala Gly Leu Thr Gly Phe His Val

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Phe 225		Gly	Gly	Val	Asn 230		Phe	Thr	Asn	G1y 235		Cys	Asn	Asn	Val 240
Ser	Arg	Val	Leu	Cys 245		Ser	Pro	Ala	Pro 250		Tyr	Leu	Gly	Arg 255	
Lys	Lys	Glu	Lys 260		Ile	Val	Ile	Arg 265		Pro	Phe	Leu	Arg 270		
Val	Ser	Asp 275		Gln	Ile	Thr	Va1 280		Ile	Met	Asp	Asn 285	Gly	Пе	Gln
G1y	G1u 290	Leu	Arg	Arg	Thr	Lys 295	Ser	Lys	Gly	Ser	Leu 300	Glu	Ile	Thr	Glu
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Ser	Arg	Tyr	Thr	G1y 325	Leu	Arg	Thr	His	Leu 330	Gly	Leu	Ala	Thr	Asn 335	Glu
Asp	Ser	Ser	Leu 340	Leu	Ala	Lys	Asp	Ser 345	Pro	Pro	Thr	Pro	Thr 350	Met	Tyr
Lys	Tyr	Arg 355	Pro	Gly	Tyr	Ser	Ser 360	Ser	Ser	Thr	Ser	A1a 365	Ala	Met	Pro
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Ser	Leu	Glu	Pro	G1u 405	Ser	Phe	Arg	Ser	Pro 410	Thr	Phe	Gly	Lys	Ser 415	
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Xaa	G1n	Gly 435	Thr	Gly	Phe	Glu	Leu 440	Gly	G1n	Leu	G1n	Ser 445	Ile	Arg	Ser
Glu	Gly 450	Thr	Thr	Ser	Thr	Ser 455	Tyr	Lys	Ser	Leu	A1a 460	Asn	Gln	Thr	Arg
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Glu	Lys	A1 a 35	Glu	Ala	Ala	Ala	Thr 40		Lys	Ala	Ala	Pro 45	Gly	Trp	Leu	
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Thr	Pro	Trp	Asn	Thr 85	Ala	Ile	Pro	Leu	Pro 90	Ser	Cys	Trp	Asp	G1n 95	Ser	
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Leu	Gly	Leu 115	Phe	Val	Glu		G1u 120		Gly	Leu	Ala	Tyr 125		۷al	Leu	
_	Lau		Tun	Trn	Mot			Clv	The	۸۸۵	Clu.		C1	C1	1	
Ser	130	FIIC	ıyı	пр	met	135	vai	uiy	1111	Arg	140	Pro	GIU	ulu	Lys	

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			ctc Leu													144
gaa Glu	aaa Lys 50	tat Tyr	aga Arg	tcc Ser	atc Ile	cgg Arg 55	att Ile	gga Gly	aac Asn	aca Thr	gcc Ala 60	ttt Phe	tct Ser	act Thr	aga Arg	192
			gtc Val													240
			gaa Glu													288
cag G1n	ctg Leu	caa Gln	aaa Lys 100	att Ile	cgt Arg	gac Asp	ctg Leu	att Ile 105	gcc Ala	ata Ile	gag Glu	Arg	agt Ser 110	agc Ser	aga Arg	336

	Ser	-	agc Ser	Lys			_	cct Pro	384
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Asn			aac Asn						480
			gct Ala			-	-	_	528
			ctg Leu						576
			ccg Pro						624
			aga Arg 215						672
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Glu	Glu	Gly	Glu	Thr 85	His	Leu	Ile	Phe	Pro 90	Lys	Lys	A٦a	Ser	Va1 95	Glu	
Gln	Leu	Gln	Lys 100	Пе	Arg	Asp	Leu	Ile 105	Ala	Пe	Glu	Arg	Ser 110	Ser	Arg	
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Leu 145	Asn	G1n	His	Thr	Arg 150	Asn	Arg	Gln	Gly	G1n 155	Ser	Ser	Asp	Pro	Pro 160	
Ser	Ala	Ser	Thr	Val 165	Ala	Ala	Asp	Ser	Ala 170	Пе	Leu	Glu	Val	Leu 175	Gln	
Ser	Asn	Ile	Gln 180	His	Val	Leu	Val	Tyr 185	Glu	Asn	Pro	Ala	Leu 190	Gln	Glu	
Lys	Ala	Leu 195	Ala	Çys	He	Pro	Val 200	Gln	Glu	Leu	Lys	Arg 205	Lys	Ser	Gln	
G1u	Lys 210	Leu	Ser	Arg	Ala	Arg 215	Lys	Leu	Asp	Lys	Gly 220	Пe	Asn	Ile	Ser	
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Thr	Δra	Spr	Δra	Acn	Λna	Sar	Lau	انم ا		San	Acn	Acn			Lvc	

Trp	Gly			Glu	Val	Glu		265 His		Cys	Asp			Gln	Phe	
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WO 01/29221

PCT/US00/29052

203

				-	_						aat Asn 125					384
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_		-		-		_	_			-	atg Met		~	~~		480
		_	-								ctt Leu		-	_		528
	_	_	-				-	-		-	cta Leu		_			576
											gtg Val 205				•	624
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Lys Leu Leu Tyr Leu Leu Glu Ser Thr Glu Asp Pro Val Ile Ile Glu
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Arg Ala Leu Ile Thr Leu Gly Asn Asn Ala Ala Phe Ser Val Asn Gln
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Ala Ile Ile Arg Glu Leu Gly Gly Ile Pro Ile Val Ala Asn Lys Ile
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Asn His Ser Asn Gln Ser Ile Lys Glu Lys Ala Leu Asn Ala Leu Asn
        115
                           120
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Asn Leu Ser Val Asn Val Glu Asn Gln Ile Lys Ile Lys Val Gln Val
Leu Lys Leu Leu Leu Asn Leu Ser Glu Asn Pro Ala Met Thr Glu Gly
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Leu Leu Arg Ala Gln Val Asp Ser Ser Phe Leu Ser Leu Tyr Asp Ser
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His Val Ala Lys Glu Ile Leu Leu Arg Val Leu Thr Leu Phe Gln Asn
           180
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Ile Lys Asn Cys Leu Lys Ile Glu Gly His Leu Ala Val Gln Pro Thr
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Phe Thr Glu Gly Ser Leu Phe Phe Leu Leu His Gly Glu Glu Cys Ala
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336			tcc Ser								
384			gac Asp								
432			acc Thr 140								
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			ggc Gly													672
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			cag G1n													768
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Glu Trp Lys Gly Trp Ser Lys Pro Ser Asp Ser Pro Ala Ala Leu Glu
Ser Ala Phe Ser Ser Tyr Ser Asp Leu Ser Glu Gly Glu Gln Glu Ala
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                                        75
Arg Phe Ala Ala Gly Val Ala Glu Gln Phe Ala Ile Ala Glu Ala Lys
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Leu Arg Ala Trp Ser Ser Val Asp Gly Glu Asp Ser Thr Asp Asp Ser
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Tyr Asp Glu Asp Phe Ala Gly Gly Met Asp Thr Asp Met Ala Gly Gln
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Leu Pro Leu Gly Pro His Leu Gln Asp Leu Phe Thr Gly His Arg Phe
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Ser Arg Pro Val Arg Gln Gly Ser Val Glu Pro Glu Ser Asp Cys Ser
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Gln Thr Val Ser Pro Asp Thr Leu Cys Ser Ser Leu Cys Ser Leu Glu
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                165
Asp Gly Leu Leu Gly Ser Pro Ala Arg Leu Ala Ser Gln Leu Leu Gly
Asp Glu Leu Leu Ala Lys Leu Pro Pro Ser Arg Glu Ser Ala Phe
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Arg Ser Leu Gly Pro Leu Glu Ala Gln Asp Ser Leu Tyr Asn Ser Pro
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Leu Thr Glu Ser Cys Leu Ser Pro Ala Glu Glu Glu Pro Ala Pro Cys
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Lys Asp Cys Gln Pro Leu Cys Pro Pro Leu Thr Gly Ser Trp Glu Arg
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											caa Gln 125			384
Val		Leu	Val	Gly	Arg	Leu	Gly	Gly	Leu	Ser	aca Thr			432
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		gtg Val 180	-	-						_	-	•	576
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		ctg Leu				 _	_	_					768
		gag G1u 260					-						816
		cca Pro											864
		agc Ser						-		_			912
		cac His											960
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Ser	Leu	Val	Asp 100		Leu	Gly	Arg	Lys 105		Ser	Cys	۷a٦	Leu 110		Ser
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Ile	Pro 370	Glu	Thr	Glu	Gln	A1a 375	Gly	Val	Leu	Asn	Trp 380	Phe	Arg	Val	Pro
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1 Leu Ala Leu Cys 65	Ala Tyr Leu Val 50 Ser	Gly Gln Ala 35 Leu Ser	Pro Ala 20 Arg Arg Leu	·5 Ala Phe Arg Leu Gln	His Tyr Asp Val 70	Cys Cys Pro 55 Pro	Val Tyr 40 Ser Gly	Leu 25 Thr Val	10 Ala Glu Lys Thr	Gln Arg Arg Cys 75	Asp Thr Thr 60	Pro Ile 45 Leu Gln	Glu 30 Ala Cys Arg	15 Asn Lys Arg Gln Cys	Gln Xaa Gly Arg 80	
1 Leu Ala Leu Cys 65 Arg	Ala Tyr Leu Val 50 Ser Cys	Gly Gln Ala 35 Leu Ser Arg	Pro Ala 20 Arg Arg Leu Gly Arg	·5 Ala Phe Arg Leu Gln 85	His Tyr Asp Val 70 Arg	Cys Cys Pro 55 Pro Trp	Val Tyr 40 Ser Gly Thr	Leu 25 Thr Val Leu Val	10 Ala Glu Lys Thr Gln 90	Gln Arg Arg Cys 75 Thr	Asp Thr Thr 60 Thr	Pro Ile 45 Leu Gln Leu	Glu 30 Ala Cys Arg Thr	15 Asn Lys Arg Gln Cys 95	Gln Xaa Gly Arg 80 Gln	
1 Leu Ala Leu Cys 65 Arg	Ala Tyr Leu Val 50 Ser Cys	Gly Gln Ala 35 Leu Ser Arg Gln Glu	Pro Ala 20 Arg Arg Leu Gly Arg 100	Phe Arg Leu Gln 85 Phe	His Tyr Asp Val 70 Arg Leu	Cys Cys Pro 55 Pro Trp Asn	Val Tyr 40 Ser Gly Thr Asp	Leu 25 Thr Val Leu Val Pro 105	10 Ala Glu Lys Thr Gln 90 Gly	Gln Arg Arg Cys 75 Thr	Asp Thr Thr 60 Thr	Pro Ile 45 Leu Gln Leu Leu Lys	Glu 30 Ala Cys Arg Thr	15 Asn Lys Arg Gln Cys 95 Gly	Gln Xaa Gly Arg 80 Gln Asp	
1 Leu Ala Leu Cys 65 Arg Arg	Ala Tyr Leu Val 50 Ser Cys Ser	Gly Gln Ala 35 Leu Ser Arg Gln Glu 115	Pro Ala 20 Arg Arg Leu Gly Arg 100 Ala	Phe Arg Leu Gln 85 Phe Gln	His Tyr Asp Val 70 Arg Leu	Cys Cys Pro 55 Pro Trp Asn Gly	Val Tyr 40 Ser Gly Thr Asp Ser 120	Leu 25 Thr Val Leu Val Pro 105 Gln	10 Ala Glu Lys Thr Gln 90 Gly	Gln Arg Arg Cys 75 Thr His	Asp Thr Thr 60 Thr Cys Leu	Pro Ile 45 Leu Gln Leu Lys 125	Glu 30 Ala Cys Arg Thr Trp 110 Pro	15 Asn Lys Arg Gln Cys 95 Gly Leu	Gln Xaa Gly Arg 80 Gln Asp	

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		gcc Ala 35															144
		gta Val															192
acc Thr 65	gcc Ala	acc Thr	agg Arg	aat Asn	ggc Gly 70	ạcc Thr	ctg Leu	cct Pro	gga Gly	ccc Pro 75	agc Ser	999 Gly	aac Asn	atc Ile	cgc Arg 80		240
999 Gly	gtg Val	gtg Val	tgc Cys	cgg Arg 85	ctg Leu	tcc Ser	agg Arg	agc Ser	ctc Leu 90	cag Gln	gag Glu	cac His	cat His	999 Gly 95	ctc Leu		288
ccg Pro	cct Pro	gct Ala	gga Gly 100	ctt Leu	tgc Cys	cgc Arg	cag Gln	cca Pro 105	gcc Ala	aaa Lys	gca Ala	cgt Arg	cct Pro 110	caa Gln	gac Asp	;	336
gct Ala	cca Pro	gga Gly 115	act Thr	ctt Leu	aga Arg	Leu	aga Arg 120	gtc Val	ctt Leu	999 Gly	agg Arg	cag Gln 125	ccg Pro	caa Gln	ggc Gly	(384
cac	tga															3	390

215

His *

<210> 150
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<212> PRT
<213> Homo sapiens
<400> 150
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120

125

<210> 151 <211> 567 <212> DNA <213> Homo sapiens <220>

115

His

<220> <221> CDS <222> (1)...(567)

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Met Val Pro Ala Pro Gln His Val Thr Glu Leu Glu Leu Gly Met Tyr
1 5 10 15

gcc ctg ctg gga gtc ttc tgc gtg gcc atc ttc atc ttc ttg gtc aat

Ala	Leu	Leu	Gly 20		Phe	Cys	۷a۱	A1 a 25		Phe	Ile	Phe	Leu 30		Asn	
			Phe					G1n					Pro		agt Ser	144
gcc Ala	act Thr 50	gac Asp	ccc Pro	acc Thr	tcc Ser	ccc Pro 55	cag Gln	ccc Pro	cac His	aac Asn	tgg Trp 60	Val	tgg Trp	ctg Leu	ggc Gly	192
act Thr 65	gac Asp	cag Gln	gag Glu	gaa Glu	ctg Leu 70	agc Ser	cgc Arg	cag Gln	ctg Leu	gac Asp 75	cgg Arg	cag Gln	tcc Ser	cct Pro	ggc Gly 80	240
ccg Pro	ccc Pro	aag Lys	ggg Gly	gag Glu 85	ggg Gly	agc Ser	tgc Cys	ccc Pro	tgt Cys 90	gag Glu	agt Ser	999 Gly	gga Gly	gga Gly 95	ggg Gl <i>y</i>	288
gag Glu	gcc Ala	cct Pro	acc Thr 100	ctg Leu	gcc Ala	cct Pro	ggc Gly	cct Pro 105	cct Pro	ggg Gly	ggc Gly	acc Thr	acc Thr 110	agc Ser	tcc Ser	336
tca Ser	agc Ser	acc Thr 115	ctg Leu	gcc Ala	cga Arg	aag Lys	gag Glu 120	gct Ala	999 Gly	999 Gly	cgg Arg	cgg Arg 125	aag Lys	cga Arg	gta Val	384
gag Glu	ttt Phe 130	gtg Val	aca Thr	ttt Phe	gcg Ala	cca Pro 135	gcc Ala	cct Pro	cca Pro	gcc Ala	cag G1n 140	tca Ser	cct Pro	gag Glu	gag G1u	432
oct Pro 145	gta Val	999 Gly	gcc Ala	cct Pro	gct Ala 150	gtg Val	cag Gln	tcc Ser	atc Ile	ctt Leu 155	gtg Val	gca Ala	ggc Gly	gag Glu	gag Glu 160	480
gac Asp	atc Ile	cgc Arg	tgg Trp	gtg Val 165	tgt Cys	gag Glu	gac Asp	atg Met	999 Gly 170	ctg Leu	aag Lys	gac Asp	cct Pro	gag Glu 175	gag Glu	528
		Asn	tac Tyr 180									tga *				567

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      <212> PRT
      <213> Homo sapiens
      <400> 152
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Ala Leu Leu Gly Val Phe Cys Val Ala Ile Phe Ile Phe Leu Val Asn
Gly Val Val Phe Val Leu Arg Tyr Gln Arg Lys Glu Pro Pro Asp Ser
Ala Thr Asp Pro Thr Ser Pro Gln Pro His Asn Trp Val Trp Leu Gly
                        55
                                            60
Thr Asp Gln Glu Glu Leu Ser Arg Gln Leu Asp Arg Gln Ser Pro Gly
Pro Pro Lys Gly Glu Gly Ser Cys Pro Cys Glu Ser Gly Gly Gly
                                    90
Glu Ala Pro Thr Leu Ala Pro Gly Pro Pro Gly Gly Thr Thr Ser Ser
            100
                                105
Ser Ser Thr Leu Ala Arg Lys Glu Ala Gly Gly Arg Arg Lys Arg Val
                            120
                                                125
Glu Phe Val Thr Phe Ala Pro Ala Pro Pro Ala Gln Ser Pro Glu Glu
                        135
                                            140
Pro Val Gly Ala Pro Ala Val Gln Ser Ile Leu Val Ala Gly Glu Glu
                    150
                                        155
Asp Ile Arg Trp Val Cys Glu Asp Met Gly Leu Lys Asp Pro Glu Glu
                165
                                   170
Leu Arg Asn Tyr Met Glu Arg Ile Arg Gly Ser Ser
            180
                                185
      <210> 153
      <211> 735
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      <221> CDS
      <222> (1)...(735)
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Met Ala Thr Gly Thr Arg Tyr Ala Gly Lys Val Val Val Thr Gly
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				Ile					· Val					Asn	agc Ser	96
ggg Gly	gcc Ala	cga Arg 35	Val	gtt Val	atc Ile	tgc Cys	gac Asp 40	Lys	gat Asp	gag Glu	tct Ser	ggg Gly 45	Gly	cgg Arg	gcc Ala	144
		Gln										Cys			act Thr	192
cag G1n 65	gaa Glu	gat Asp	gat Asp	gtg Val	aag Lys 70	acc Thr	ctg Leu	gtt Val	tct Ser	gag Glu 75	acc Thr	atc Ile	cgc Arg	cga Arg	ttt Phe 80	240
ggc Gly	cgc Arg	ctg Leu	gat Asp	tgt Cys 85	gtt Val	gtc Val	aac Asn	aac Asn	gct Ala 90	ggc Gly	cac His	cac His	cca Pro	ccc Pro 95	cca Pro	288
												cag Gln				336
												gcc Ala 125				384
												agc Ser				432
												acc Thr				480
gta /al	aca Thr	gcc Ala	atg Met	acc Thr 165	aaa Lys	gct Ala	ttg Leu	gcc Ala	ctg Leu 170	gat Asp	gaa Glu	agt Ser	cca Pro	tat Tyr 175	ggt Gly	528
itc 'al	cga Arg	gtc Val	aac Asn 180	tgt Cys	atc Ile	tcc Ser	Pro	gga Gly 185	aac Asn	atc Ile	tgg Trp	acc Thr	ccg Pro 190	ctg Leu	tgg Trp	576

								gcc Ala			624
								agc Ser 220			672
								act Thr			720
_	aac Asn	-	_	tga *							735

<211> 244

<212> PRT

<213> Homo sapiens

<400> 154

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۷a٦	Thr	· Alá	Met	: Thr 165		Ala	l Leu	ı Ala	a Leu 170		G]ı	ı Ser	Pro	Tyr 175	Gly	
Val	Arg	Val	Asn 180	Cys		e Ser	Pro	رG و 185		Ιle	e Trp	Thr	Pro	Leu	, Trp	
GΊι	ı Glu	Leu 195		Ala	Leu	ı Met	Pro 200	Asp		Arg	ı Ala	Thr 205	Ile		, Glu	
Gly	Met 210		ı Pro	Ser	His	Trp 215		Ala	1 Trp	Ala	Ser 220	Pro		Arg	Ser	
225	,				Ser 230		Pro	Pro	Lys	Pro 235		Ser	Ala	Arg	Ala 240	
Leu	Asn	Cys	Ser													
	<, <,	211> 212>	155 975 DNA Home		pien	S										
	<		CDS	(9	975)											
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aca Thr	tgg Trp	gcc Ala	gag Glu 20	ggc Gly	atg Met	ggc Gly	ctg Leu	ggc Gly 25	ccc Pro	cct Pro	gag G1u	ctg Leu	tca Ser 30	999 Gly	tca Ser	96
gcc Ala	tct Ser	ccc Pro 35	agc Ser	cgg Arg	tac Tyr	cat His	999 Gly 40	cct Pro	gcc Ala	cgc Arg	tgg Trp	atg Met 45	ccc Pro	cca Pro	cgc Arg	144
tgg Trp	gcc Ala 50	cag Gln	ggt Gly	gcc Ala	cct Pro	gag Glu 55	ctg Leu	gag Glu	cag Gln	gaa Glu	cgc Arg 60	cgg Arg	cac His	cgg Arg	cag Gln	192
att	gtg	tcc	tgg	ttc	gcc	gac	cac	ccc	cgg	gcc	CCC	ttt	ggc	cta	cac	240

	Ile 65		Ser	`Trp	Phe	A1a 70		His	Pro	Arg	Ala 75		Phe	Gly	Leu	His 80	
	cgg Arg	ctg Leu	gtg Val	gag Glu	ctt Leu 85	999 Gly	cag Gln	agc Ser	tca Ser	ggc Gly 90	Lys	aag Lys	gca Ala	ggt Gly	gac Asp 95	tgg Trp	288
					Leu	gtg Val											336
				Val		cgc Arg											384
,			Lys			gtg Val											432
						gtg Val 150											480
	gag Glu	act Thr	ctc Leu	aac Asn	ccc Pro 165	gtg Val	tat Tyr	gtg Val	ccc Pro	tgc Cys 170	gtg Val	aag Lys	gaa Glu	ctc Leu	ctg Leu 175	cgt Arg	528
	tgc Cys	gag Glu	ctg Leu	tgc Cys 180	ctg Leu	ggc Gly	atc Ile	atg Met	ggt Gly 185	ggg Gly	aaa Lys	ccg Pro	cga Arg	cac His 190	tca Ser	ctg Leu	576
						caa Gln	Asp										624
	Tyr	tgc Cys 210	cag Gln	ccc Pro	act Thr	gtg Val	gat Asp 215	gtc Val	agc Ser	cag G1n	Ala	gac Asp 220	ttc Phe	ccc Pro	ctg Leu	gag Glu	672
	tcc Ser 225	ttc Phe	cac His	tgc Cys	Thr	tcg Ser 230	ccc Pro	cgc Arg	aag Lys	Met	gcc Ala 235	ttt Phe	gcc Ala	aag Lys	atg Met	gac _. Asp 240	720
	сса	agc	tgt	acc	gtg	ggc	ttc	tat	gct	gga	gac	agg	aag	gag	ttt	gag	768

Pro	Ser	Cys	Thr	Va1 245	Gly	Phe	Tyr	Ala	G1y 250	Asp	Arg	Lys	Glu	Phe 255	Glu		
			tca Ser 260													8	16
gag Glu	cgg Arg	tac Tyr 275	ccc Pro	atg Met	ttc Phe	acc Thr	ctg Leu 280	gcc Ala	gag Glu	ggc Gly	cat His	gct Ala 285	cag Gln	gac Asp	cac His	8	64
			gac Asp													9	12
			999 Gly	Arg												90	50
	gtg Val		tta Leu	taa *												97	75

<211> 324

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

<222> (1)...(324)

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<400> 156

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Thr Trp Ala Glu Gly Met Gly Leu Gly Pro Pro Glu Leu Ser Gly Ser 20 25 30

Ala Ser Pro Ser Arg Tyr His Gly Pro Ala Arg Trp Met Pro Pro Arg 35 40 45

Trp Ala Gln Gly Ala Pro Glu Leu Glu Gln Glu Arg Arg His Arg Gln 50 55 60

Ile Val Ser Trp Phe Ala Asp His Pro Arg Ala Pro Phe Gly Leu His

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65
                    70
Arg Leu Val Glu Leu Gly Gln Ser Ser Gly Lys Lys Ala Gly Asp Trp
Tyr Gly Pro Ser Leu Val Ala His Ile Leu Arg Lys Ala Val Glu Ser
            100
                                105
Cys Ser Asp Val Thr Arg Leu Val Val Tyr Val Ser Gln Asp Cys Thr
                            120
Val Tyr Lys Ala Asp Val Ala Arg Leu Val Ala Arg Pro Asp Pro Thr
                        135
Ala Glu Trp Lys Ser Val Val Ile Leu Val Pro Val Arg Leu Gly Gly
                    150
                                        155
Glu Thr Leu Asn Pro Val Tyr Val Pro Cys Val Lys Glu Leu Leu Arg
                                   170
Cys Glu Leu Cys Leu Gly Ile Met Gly Gly Lys Pro Arg His Ser Leu
            180
                                185
Tyr Phe Ile Gly Tyr Gln Asp Asp Phe Leu Leu Tyr Leu Asp Pro His
                            200
Tyr Cys Gln Pro Thr Val Asp Val Ser Gln Ala Asp Phe Pro Leu Glu
                        215
Ser Phe His Cys Thr Ser Pro Arg Lys Met Ala Phe Ala Lys Met Asp
                    230
                                        235
Pro Ser Cys Thr Val Gly Phe Tyr Ala Gly Asp Arg Lys Glu Phe Glu
                245
                                    250
Thr Leu Cys Ser Glu Leu Thr Arg Val Leu Ser Ser Ser Ala Thr
            260
                               265
Glu Arg Tyr Pro Met Phe Thr Leu Ala Glu Gly His Ala Gln Asp His
       275
                            280
Ser Leu Asp Asp Leu Cys Ser Gln Leu Ala Gln Pro Thr Leu Arg Leu
                       295
Pro Arg Thr Gly Arg Leu Leu Arg Ala Lys Arg Pro Ser Ser Glu Asp
                   310
                                       315
Phe Val Phe Leu
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<211> 669

<212> DNA

<213> Homo sapiens

<220>

<221> CDS

<222> (1)...(669)

<400> 157

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aag Lys	tct Ser	att	att Ile 20	Ser	aga Arg	aga Arg	ttt Phe	tto Phe 25	Cys	ata Ile	gtt Val	ggc Gly	acg Thr	Lei	ıtac ıTyr	96
ctg Leu	tat Tyr	cgg Arg 35	Cys	att Ile	aca Thr	atg Met	tat Tyr 40	Val	act Thr	aca Thr	ctc Leu	cca Pro 45	Val	cct Pro	ggt	144
atg Met	cat His 50	Phe	aac Asn	tgt Cys	tct Ser	ccg Pro 55	aag Lys	ctt Leu	ttc Phe	gga Gly	gac Asp 60	tgg Trp	gaa Glu	gcc Ala	caa Gln	192
ctg Leu 65	cga Arg	aga Arg	ata Ile	atg Met	aag Lys 70	ctc Leu	att Ile	gct Ala	gga Gly	ggt Gly 75	ggc Gly	ttg Leu	tct Ser	atc Ile	act Thr 80	240
ggc Gly	tct Ser	cac His	aac Asn	atg Met 85	tgt Cys	ggg Gly	gac Asp	tat Tyr	ctg Leu 90	tac Tyr	agc Ser	ggc Gly	cac His	acg Thr 95	gtc Val	288
						tta Leu										336
ctc Leu	tgg Trp	tgg Trp 115	tat Tyr	cac His	tgg Trp	att Ile	tgc Cys 120	tgg Trp	ctt Leu	ctc Leu	agc Ser	gta Val 125	gtt Val	gga Gly	atc Ile	384
Phe	tgt Cys 130	att Ile	ctc Leu	tta Leu	gcg Ala	cat His 135	gac Asp	cac His	tac Tyr	act Thr	gtg Val 140	gac Asp	gtg Val	gtg Val	gtg Val	432
gca 11a 145	tat Tyr	tac Tyr	atc Ile	acc Thr	acg Thr 150	aga Arg	ctc Leu	ttc Phe	Trp	tgg Trp 155	tat Tyr	cac His	act Thr	atg Met	gcc Ala 160	480
aat (\sn (cag Gln	caa G1n	gtg Val	cta Leu 165	aag Lys	gaa Glu	gct Ala	Ser	cag G1n 170	atg Met	aac Asn	ctc Leu	ctg Leu	gcc Ala 175	agg Arg	528

gtg tgg tgg tac agg cca ttt cag tac ttt gaa aag aat gtc ca Val Trp Trp Tyr Arg Pro Phe Gln Tyr Phe Glu Lys Asn Val Gi 180 185 190	aa gga 576 n Gly
att gta cct cga tct tac cat tgg cct ttc ccc tgg cca gta gt Ile Val Pro Arg Ser Tyr His Trp Pro Phe Pro Trp Pro Val Va 195 200 205	ccac 624 11 His
ctc agt agg caa gtt aaa tac agc cgg ctg gtg aat gac aca ta Leu Ser Arg Gln Val Lys Tyr Ser Arg Leu Val Asn Asp Thr * 210 215 220	
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Lys Ser Ile Ile Ser Arg Arg Phe Phe Cys Ile Val Gly Thr Lei	ı Tyr
Leu Tyr Arg Cys Ile Thr Met Tyr Val Thr Thr Leu Pro Val Pro	o Gly
Met His Phe Asn Cys Ser Pro Lys Leu Phe Gly Asp Trp Glu Ala 50 55 60	a Gln
Leu Arg Arg Ile Met Lys Leu Ile Ala Gly Gly Gly Leu Ser Ile 65 70 75	Thr 80
Gly Ser His Asn Met Cys Gly Asp Tyr Leu Tyr Ser Gly His Thr 85 90 95	· Val
Met Leu Thr Leu Thr Tyr Leu Phe Ile Lys Glu Tyr Ser Pro Arg 100 105 110	, Arg
Leu Trp Trp Tyr His Trp Ile Cys Trp Leu Leu Ser Val Val Gly 115 120 125	' Ile
Phe Cys Ile Leu Leu Ala His Asp His Tyr Thr Val Asp Val Val 130 135 140	Val
Ala Tyr Tyr Ile Thr Thr Arg Leu Phe Trp Trp Tyr His Thr Met 145 150 155	Ala 160
Asn Gln Gln Val Leu Lys Glu Ala Ser Gln Met Asn Leu Leu Ala 165 170 175	Arg
Val Trp Trp Tyr Arg Pro Phe Gln Tyr Phe Glu Lys Asn Val Gln 180 185 190	Gly
Ile Val Pro Arg Ser Tyr His Trp Pro Phe Pro Trp Pro Val Val	His

Leu	Ser 210			n Vai	l Lys	Tyr 215) Lei	ı Va	l Asr 220	•		7		
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	<		CDS		540)											
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ctg Leu	ctc Leu	cta Leu	gcc Ala 20	tcg Ser	cag G1n	gtc Val	ctg Leu	tct Ser 25	ccg Pro	gga Gly	agc Ser	tgc Cys	gcg Ala 30	gac Asp	gag Glu	96
gag Glu	gag G1u	gtc Val 35	ccc Pro	gag G1u	gag Glu	tgg Trp	gtg Val 40	ctc Leu	ctg Leu	cac His	gtc Val	gtc Val 45	cag Gln	ggc Gly	cag G1n	144
ata Ile	ggc Gly 50	gcc Ala	ggg Gly	aac Asn	tac Tyr	agc Ser 55	tac Tyr	ctg Leu	cgg Arg	ctg Leu	aac Asn 60	cac His	gag Glu	ggc Gly	aag Lys	192
ata Ile 65	gtc Val	ctc Leu	agg Arg	atg Met	cgc Arg 70	acc Thr	tnc Xaa	aag Lys	gga Gly	gat Asp 75	gcg Ala	gat Asp	ctg Leu	tac Tyr	gtc Val 80	240
tcc Ser	gcc Ala	agc Ser	agc Ser	ctg Leu 85	cac His	ccc Pro	agc Ser	ttc Phe	gac Asp 90	gac Asp	tac Tyr	gag Glu	ctg Leu	caa Gln 95	tcg Ser	288
gcc Na	acc Thr	tgn Xaa	cgg Arg	ccc Pro	gga Gly	cgc Arg	cgt Arg	gtc Val	cat His	ccc Pro	cgc Arg	gca Ala	ctt Leu	ccg Pro	gcg Ala	336

			100					105	•				110)		
			His					Thr					Gly		g cga ı Arg	384
gtt Val	cga Arg 130	gat Asp	gaa Glu	ggt Gly	gta Val	cta Leu 135	cga Arg	cgg Arg	cac	ggt Gly	ncg Xaa 140	Ser	agc Ser	acc Thr	cgt Arg	432
tcg Ser 145	Ala	agg Arg	ccg Pro	cct Pro	acc Thr 150	ccg Pro	ccg Pro	acg Thr	gcg Ala	cag Gln 155	Met	ccg Pro	gcc Ala	aga Arg	agc Ser 160	480
acg Thr	ctg Leu	gtg Val	ccc Pro	cgg Arg 165	aag Lys	acg Thr	cct Pro	cgc Arg	aag Lys 170	agg Arg	agg Arg	aat Asn	ctg Leu	ttc Phe 175	Ser	528
	cga Arg		taa *													540
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Leu	Leu	Leu	A1a 20	Ser	Gln	Val		Ser 25		Gly	Ser	Cys	Ala 30		Glu	
Glu		Val 35		Glu	Glu				Leu	His	Val	Va1 45		G1y	Gln	
Ile			G1y	Asn	Tyr			Leu	Arg	Leu	Asn 60		Glu	Gly	Lys	
Ile 65		Leu	Arg	Met	Arg 70		Xaa	Lys	Gly	Asp 75		Asp	Leu	Tyr	Va1 80	

Ser	Ala	Ser	· Ser	Leu 85	ı His	Pro	Ser	Phe	Asp 90) Asp) Tyr	· Glu	ı Lei	Glr 95	Ser	
Ala	Thr	Xaa	Arg 100		Gly	' Arg	Arg	Val 105		Pro	Arg	Ala	Leu 110	Pro	Ala	
Pro	Ser	Gly 115		Arg	Arg	Leu	Trp 120		Pro	Lei	ı Pro	Pro 125	Gly		Arg	
Val	Arg 130		Glu	Gly	Val	Leu 135		Arg	His	Gly	′ Xaa 140	Ser		Thr	Arg	
Ser 145	Ala	Arg	Pro	Pro	Thr 150	Pro		Thr	Ala	Gln 155	Met		Ala	Arg	Ser 160	
Thr	Leu	۷a۱	Pro	Arg 165		Thr	Pro	Arg	Lys 170	Arg		Asn	Leu	Phe 175	Ser	
Gly	Arg	Tyr												2,0		
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999 Gly	ccc Pro	ggc Gly 35	gcg Ala	gcc Ala	tac Tyr	cac His	atg Met 40	ttc Phe	gtg Val	gtg Val	atg Met	gag Glu 45	gac Asp	ttg Leu	gtg Vajl	144
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aac Asn 65	ctg Leu	aag Lys	gcc Ala	ccg Pro	tcc Ser 70	aga Arg	cac His	tat Tyr	ttt Phe	gca Ala 75	ctg Leu	cct Pro	acc Thr	aac Asn	cct Pro 80	240

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				gca Ala	-						_	_	576
				aca Thr							-		624
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				gaa G1u									720
		Glu		cta Leu			-	_	_				768

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								agc Ser 365			1104
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G1n 385	Glu	Thr	Val	Glu	Met 390		Ile	Arg	Ile	G1y 395		Val	Glu	His	Thr 400	
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			gcc Ala		Glu										Tyr	288
			ttg Leu 100		_			-	Gly			-	_	Āla	_	336
			aag Lys													384
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Ala		Ile 35	Arg	Arg	Cys				Ala	Ser	Ser	Asp 45		Ser	Pro	
Gly	Ser 50	Lys	Cys	Ser		G1u 55	Asp	Leu	Ala	Thr	A1a 60		Asn	Asn	Arg	
31y 55		Пе	Lys				Val	Asp		Tyr 75		Ala	Met	Asp	Asp 80	
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Thr	Leu 130		Leu	Lys	G1n	Thr 135	Пe		Asp	Lys	Glu 140	Glu		Gln	Arg	
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											acc Thr					144
											agt Ser 60					192
tat Tyr 65	aat Asn	gcc Ala	cct Pro	tct Ser	ctc Leu 70	aag Lys	gag Glu	tgg Trp	ata Ile	gat Asp 75	gtc Val	att Ile	cac His	aag Lys	cac His 80	240
											tca Ser					288
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gtc Val	gta Val 130	Gly	cag Gln	ttt Phe	tca Ser	agc Ser 135	gtt Val	ggc Gly	tcc Ser	ttg Leu	gga Gly 140	Ala	gat Asp	gaa Glu	tca Ser	432
aag Lys 145	tgg Trp	tta Leu	tgt Cys	tct Ser	gag Glu 150	ttt Phe	aaa Lys	gag Glu	agc Ser	atg Met 155	Leu	aca Thr	ctg Leu	999 Gly	aag Lys 160	480
	agc Ser															528
	tct Ser															576
ggc Gly	tct Ser	ctt Leu 195	ccc Pro	tat Tyr	agc Ser	atc Ile	cag G1n 200	aca Thr	gct Ala	gaa Glu	aaa Lys	cag Gln 205	aat Asn	tgg Trp	ctg Leu	624
	tcc Ser 210															672
gcc Ala 225	atg Met	cca Pro	cat His	att Ile	aag Lys 230	aca Thr	tat Tyr	atg Met	agg Arg	cct Pro 235	tct Ser	cca Pro	gac Asp	ttc Phe	agt Ser 240	720
	att Ile							Ser								768
	gga Gly	Ala					Gly									816
ag	ctc	ggg	gtc	ctt	ttc	ctc	cct	tca	qca	ttt	agt	cta	qac	aat	ttc	864

GΊι	ı Leu	Gly 275		Leu	Phe	Leu	Pro 280		Ala	Phe	Gly	Leu 285		Ser	Phe	
		Lys				ttc Phe 295						Pro				912
	Pro					ttg Leu										960
						att Ile				Lys						1008
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	ASN	Leu	Пе	5		Asp		His	10				Gly	15		
Leu		Pro	11e 20	5 His	Ala	Asp Arg	Trp Ile	His 25	10 G1n	Lys	Thr	Gln His	G1 <i>y</i> 30	15 I1e	Trp	
	Ser Ser	Pro 35	Ile 20 Leu	5 His Tyr	Ala Pro	Asp Arg Lys	Trp Ile 40	His 25 Ala	10 Gln Asp	Lys Gly	Thr Thr Ser	Gln His 45	Gly 30 Lys	15 Ile Ser	Trp Gly	
Glu	Ser Ser 50	Pro 35 Pro	Ile 20 Leu Thr	5 His Tyr His	Ala Pro Phe Leu	Asp Arg	Trp Ile 40 Ala	His 25 Ala Asp	10 Gln Asp Leu	Lys Gly Ile Asp	Thr Thr Ser 60	Gln His 45 Tyr	Gly 30 Lys Leu	15 Ile Ser Met	Trp Gly Ala His	
Glu Tyr 65	Ser Ser 50 Asn	Pro 35 Pro Ala	Ile 20 Leu Thr Pro Glu	5 His Tyr His Ser	Ala Pro Phe Leu 70	Asp Arg Lys 55	Trp Ile 40 Ala Glu	His 25 Ala Asp Trp Leu	10 Gln Asp Leu Ile Ile	Lys Gly Ile Asp 75	Thr Thr Ser 60 Val	Gln His 45 Tyr Ile	Gly 30 Lys Leu His	15 Ile Ser Met Lys Gly	Trp Gly Ala His 80	
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Glu Tyr 65 Asp Phe	Ser Ser 50 Asn Leu Gln	Pro 35 Pro Ala Ser Gly	Ile 20 Leu Thr Pro Glu Ser 100	5 His Tyr His Ser Thr 85 Gln	Ala Pro Phe Leu 70 Asn	Asp Lys 55 Lys Val Asp	Trp Ile 40 Ala Glu Tyr	His 25 Ala Asp Trp Leu Trp 105	10 Gln Asp Leu Ile Ile 90 Gly	Lys Gly Ile Asp 75 Gly His	Thr Thr Ser 60 Val Ser Phe	Gln His 45 Tyr Ile Thr	Gly 30 Lys Leu His Pro Leu 110	15 Ile Ser Met Lys Gly 95 Lys	Trp Gly Ala His 80 Arg	

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Glu	Ser	Lys	Thr	Pro 165	Gly	Lys	Ser	Ser	Val 170	Pro		ı Tyr	Leu	I1e 175	Tyr	
Pro	Ser	۷al	G]ս 180		Val	Arg	Thr	Ser 185		G1u	Gly	Tyr	Pro 190	Ala	Gly	
Gly	Ser	Leu 195		Tyr	Ser	Пe	G1n 200	Thr	Ala	Glu	Lys	Gln 205	Asn		Leu	
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225					230					235					240	
	Пe			245					250				-	255		
	Gly		260					265					270			
	Leu	275					280					285	·			
	Val 290					295					300	•	• •			
305	Pro				310				•	315					320	
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			_ 0					20					JU			

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		Thr		tgc Cys								Tyr				192
gac Asp 65	ctg Leu	acc Thr	ttg Leu	ctt Leu	atc Ile 70	acc Thr	gag Glu	agg Arg	cag Gln	cag Gln 75	aag Lys	cac His	tgc Cys	ctg Leu	gcc Ala 80	240
				acc Thr 85												288
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tac Tyr	ctg Leu	tac Tyr 115	cgc Arg	cgg 'Arg	cgc Arg	cag Gln	cag Gln 120	ctc Leu	cag Gln	agc Ser	cca Pro	ttt Phe 125	gaa Glu	ggc Gly	cag G1n	384
				aca Thr												432
				gct Ala												480
				cct Pro 165				Tyr								528
cca Pro	gtc Val	tac Tyr	aac Asn 180	cct Pro	gca Ala	gct Ala	Pro	cct Pro 185	ccc Pro	tat Tyr	atg Met	cca Pro	cca Pro 190	cag Gln	ccc Pro	576
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Phe Phe Thr Phe Cys Cys Gly Thr Cys Tyr His Arg Tyr Cys Cys Arg
Asp Leu Thr Leu Leu Ile Thr Glu Arg Gln Gln Lys His Cys Leu Ala
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Phe Ser Pro Lys Thr Ile Ala Gly Ile Ala Ser Ala Val Ile Leu Phe
Val Ala Val Val Ala Thr Thr Ile Cys Cys Phe Leu Cys Ser Cys Cys
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Tyr Leu Tyr Arg Arg Arg Gln Gln Leu Gln Ser Pro Phe Glu Gly Gln
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Gln Asp Pro Lys Ala Gly Pro Ala Pro Pro Gln Pro Gly Phe Met Tyr
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Pro Pro Ser Gly Pro Ala Pro Gln Tyr Pro Leu Tyr Pro Ala Gly Pro
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			Val	acg Thr				Thr					Πe		gtc Val	144
				ctg Leu								Ala			gcg Ala	192
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				ctg Leu 85												288
				ctc Leu												336
gac Asp	tgc Cys	cac His 115	cca Pro	gga Gly	ctg Leu	ctg Leu	gat Asp 120	cct Pro	ctg Leu	gta Val	cca Pro	ctg Leu 125	gat Asp	gag Glu	999 Gly	384
ro		His	Thr	gac Asp	Cys		Phe	Asp		Thr		Ile				432
				tgg Trp												480
gct Na	cta Leu	tct Ser	Gly	tac Tyr 165	tgc Cys	tgt Cys	gtg Val	Ala	gca Ala 170	ctc Leu	act Thr	cta Leu	cgt Arg	gga Gly 175	gtt Val	528

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						cgg Arg 215						Trp		tag *			669
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Gly	Ser 50	Gly	Leu	Leu	Ser	Val 55	Ser	Val	Gly	Leu	Val 60	Ala	Leu	Leu	Ala		
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Gly	Pro	Cys	Arg 180		Asp	Gly		Gln 185		Gln	Leu	Glu	Glu 190		Thr		

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						aac Asn										144
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		Gln				gtc Val										336
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Ala Leu His Leu Leu Ala Leu Leu Phe Ser Ala Gln Lys His His Gln
20 25 30

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						aag Lys 55						Val				192
						acc Thr					Leu					240
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						atg Met										336
						gca Ala										384
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ct Ser	His	tca Ser 195	gta Val	ctc Leu	tat Tyr	atg Met	cgg Arg 200	ggc Gly	cgg Arg	ctg Leu	gct Ala	gag Glu 205	gtg Val	aag Lys	ggc Gly	624

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			aag Lys													768
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                                                 125
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Ser Ser Val Leu Lys Gln Gly Pro Met Gln Leu Trp Thr Thr Leu Glu
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Gln Ile Trp Leu Gln Ala Ala Glu Leu Phe Met Glu Gln Gln His Leu
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                                     170
Lys Glu Ala Gly Phe Cys Ile Gln Glu Ala Ala Gly Leu Phe Pro Thr
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Pro Asp Gly Val Arg Ile Met His Ser Leu Gly Leu Met Leu Ser Arg
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                                         235
Leu Gly His Lys Ser Leu Ala Gln Lys Val Leu Arg Asp Ala Val Glu
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Arg Gln Ser Thr Cys His Glu Ala Trp Gln Gly Leu Gly Glu Val Leu
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Gln Ala Gln Gly Gln Asn Glu Ala Ala Val Asp Cys Phe Leu Thr Ala
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Leu Glu Leu Glu Ala Ser Ser Pro Val Leu Pro Phe Ser Ile Ile Pro
    290
                        295
                                             300
Arg Glu Leu
305
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     <221> misc feature
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ctg Leu	cag Gln	gtg Val	cta Leu 20	gcg Ala	ctg Leu	ctg Leu	999 Gly	gcc Ala 25	gcc Ala	cat His	gaa Glu	agc Ser	gca Ala 30	Xaa	atg Met	96
												cac His 45				144
												gac Asp				192
												gtt Val				240
												gcg Ala				288
												tct Ser				336
												aca Thr 125				384
Ser												gtg Val				432
gct Ala 145	tca Ser	tca Ser	gta Val	aca Thr	atc Ile 150	aca Thr	aca Thr	act Thr	atg Met	cat His 155	tct Ser	gaa Glu	gca Ala	aag Lys	aaa Lys 160	480
gga	tca	aaa	ttt	gat	act	ggg	agc	ttt	gtt	ggt	ggt	att	gta	tta	acg	528

Gly	Ser	Lys	Phe	Asp 165	Thr	Gly	Ser	Phe	Va1 170	Gly	Gly	Ile	Val	Leu 175		
			tta Leu 180													576
			att Ile													624
taa *																627
	<	210> 211> 212> 213>	208	o sap	oiens	5										
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	<	222>	(1). Xaa	(2		nino	Acid	i								
Met 1	<; <;	222> 223> 400>	(1). Xaa	(2 = Ar	ny An					Ala	Leu	Leu	Leu		Thr	
1	<; <; Gly	222> 223> 400> Leu	(1). Xaa 176	(2 = Ar Ala 5	ny An Arg	Gly	Ala	Trp	10				Ala	15		
1 Leu	GlyGln	222> 223> 400> Leu Va1	(1). Xaa 176 Gly Leu	Ala 5 Ala	ny An Arg Leu	Gly Leu	Ala Gly	Trp Ala 25	10 Ala	His	Glu	Ser	Ala 30	15 Xaa	Met	
1 Leu Ala	<pre></pre> <pre>Gly Gln Ala</pre>	222> 223> 400> Leu Val Ser 35	(1). Xaa 176 Gly Leu 20	Ala 5 Ala Asn	ny An Arg Leu Ile	Gly Leu Glu	Ala Gly Asn 40	Trp Ala 25 Ser	10 Ala Gly	His Leu	Glu Pro	Ser His 45	Ala 30 Asn	15 Xaa Ser	Met Ser	
1 Leu Ala Ala	Gly Gln Ala Asn 50	222> 223> 400> Leu Val Ser 35 Ser	(1). Xaa 176 Gly Leu 20 Ala	Ala 5 Ala Asn Glu	Arg Leu Ile Thr	Gly Leu Glu Leu 55	Ala Gly Asn 40 Gln	Trp Ala 25 Ser His	10 Ala Gly Val	His Leu Pro	Glu Pro Ser 60	Ser His 45 Asp	Ala 30 Asn His	15 Xaa Ser Thr	Met Ser Asn	
1 Leu Ala Ala Glu 65	Gly Gln Ala Asn 50 Thr	222> 223> 400> Leu Val Ser 35 Ser	(1). Xaa 176 Gly Leu 20 Ala Thr Asn	Ala 5 Ala Asn Glu Ser	Arg Leu Ile Thr Thr	Gly Leu Glu Leu 55 Val	Ala Gly Asn 40 Gln Lys	Trp Ala 25 Ser His	10 Ala Gly Val Pro	His Leu Pro Thr 75	Glu Pro Ser 60 Ser	Ser His 45 Asp Val	Ala 30 Asn His	15 Xaa Ser Thr	Met Ser Asn Asp 80	
1 Leu Ala Ala Glu 65 Ser	Gly Gln Ala Asn 50 Thr	222> 223> 400> Leu Val Ser 35 Ser Ser	(1). Xaa 176 Gly Leu 20 Ala Thr Asn	Ala 5 Ala Asn Glu Ser Thr 85	Arg Leu Ile Thr Thr 70 Val	Gly Leu Glu Leu 55 Val	Ala Gly Asn 40 Gln Lys Thr	Trp Ala 25 Ser His Pro Met	10 Ala Gly Val Pro Lys 90	His Leu Pro Thr 75 Pro	Glu Pro Ser 60 Ser Thr	Ser His 45 Asp Val	Ala 30 Asn His Ala	15 Xaa Ser Thr Ser Ser 95	Met Ser Asn Asp 80	
1 Leu Ala Ala Glu 65 Ser Thr	<pre>< c</pre>	222> 223> 400> Leu Val Ser 35 Ser Ser Asn	(1). Xaa 176 Gly Leu 20 Ala Thr Asn Thr	Ala 5 Ala Asn Glu Ser Thr 85 Gly	Arg Leu Ile Thr Thr 70 Val	Gly Leu Glu Leu 55 Val Thr	Ala Gly Asn 40 Gln Lys Thr	Trp Ala 25 Ser His Pro Met Thr	10 Ala Gly Val Pro Lys 90 Asn	His Leu Pro Thr 75 Pro Met	Glu Pro Ser 60 Ser Thr	Ser His 45 Asp Val Ala Ser	Ala 30 Asn His Ala Ala Thr	15 Xaa Ser Thr Ser Ser 95 Thr	Met Ser Asn Asp 80 Asn Leu	

	130					135	,				140					
Ala 145	Ser	Ser	Val	Thr	Ile 150		Thr	Thr	Met	His 155		Glu	Ala	Lys	Lys 160	
Gly	Ser	Lys	Phe	Asp 165		Gly	Ser	Phe	Val 170		Gly	Ile	Val	Leu 175	Thr	
Leu	Gly	Val	Leu 180		He	Leu	Tyr	Ile 185		Cys	Lys	Met	Tyr 190	-	Ser	
Arg	Arg	Gly 195		Arg	Tyr	Arg	Thr 200		Asp	Glu	His	Asp 205		Ile	Ile	
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ata		100>		tet	cta	000	act	acc	taa	ata	962	nat	aat	~++	000	40
												Xaa				48
												gtc Val				96
												att Ile 45				144
cct Pro	ctt Leu 50	ggg Gly	ggg Gly	aaa Lys	atg Met	gct Ala 55	cca Pro	tat Tyr	tcc Ser	tct Ser	gcc Ala 60	ggc Gly	ccc Pro	agc Ser	cac His	192
												ctc Leu				240

	gtg Val				_	_	_	 -	att Ile	28	8
	gac Asp 100				Phe					33	6
	tac Tyr									38	4
	gcc Ala									43	2
	gcc Ala	_	 _	-	_		_	_	_	48	0
	gat Asp									52	8
	gcc Ala 180									57	6
	tgc Cys									624	4
	ttg Leu									672	2
	acc Thr									_. 720)
	aag Lys									768	3

agg Arg	aaa Lys	gag Glu	tct Ser 260	gtt Val	gtg Val	gtc Val	gct Ala	gtg Val 265	Arg	999 Gly	acc Thr	atg Met	tct Ser 270	ctg Leu	cag Gln	816
gat Asp	gtc Val	ctt Leu 275	Thr	gac Asp	ctg Leu	tca Ser	gcg Ala 280	gag Glu	agt Ser	gag Glu	gtg Val	ctg Leu 285	gac Asp	gtg Val	gag Glu	864
												tct Ser				912
												ttg Leu				960
												ggc Gly				1008
												aga Arg				1056
												999 Gly 365				1104
												tca Ser				1152
												ttg Leu				1200
			Пe					Ala				aaa Lys				1248
		Leu					Trp					gga Gly				1296

			Pro					Leu					Gly		acc Thr	1344
												Thr			tcc Ser	1392
	aac Asn	-														1401
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			178	_												
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Cys	Asp	Arg	Thr 20	Val	Val	Asn	Gly	Ile 25	Ile	Ala	Thr	Val	Va1 30	Val	Ser	
Trp	Ile	Ile 35		Ala	Ala	Thr	Va1 40		Ser	Пе	Ile	Ile 45		Phe	Asp	
Pro	Leu 50		Gly	Lys	Met	Ala 55		Tyr	Ser	Ser	A1a 60		Pro	Ser	His	
Leu 65		Ser	His	Asp	Ser 70	Ser	Gln	Leu	Leu			Leu	Lys	Thr		
	Thr	Ser	Val		Glu	Thr					Leu		Cys	Cys 95	80 Ile	
Gly	Lys	Asp	Asp 100			Arg			-				Ala 110		Leu	
Phe	Ser	Thr 115		Phe	Ser	Asp	Thr 120		Leu	Val	Pro	Ser 125		Пе	Ala	
Ala	Gly 130		Ala	Leu	Leu	His 135		Gln	Gln	Asp	Asn 140		Arg	Asn	Asn	
G]n 145		Pro	Ala	Gln	Val 150	Val	Cys	His	Ala	Pro 155		Ser	Ser	Gln	Glu 160	

Ala	Asp	Leu	ı Asp	Ala 165		Leu	Glu	ı Asr	Cys 170		His	Tyr	Met	Gln 175	
Ala	Ala	Ala	Ala 180	Tyr	· Gly	Trp	Pro	Leu 185		· Ile	. Tyr	' Arg	Asn 190	Pro	
Thr	Gly	Leu 195		Arg	Ile	Gly	Gly 200		Cys	Cys	Arg	Ser 205		Thr	Thr
Asp	Tyr 210		Leu	Val	Gly	Gly 215		Gln	Leu	Asn	Cys 220		Phe	Gly	Ser
225					230					235					240
				245					250		۷a٦			255	
			260					265			Thr		270		
		275					280				Val	285			
	290					295					Ile 300				
305					310					315	Ile				320
				325					330		Val			335	
			340					345			Leu		350		-
		355					360				Arg	365		•	
	370					375					Va] 380				
385					390					395	Asn			•	400
				405					410		Asn			415	-
			420					425			Phe		430		
		435					440				Gly	445			
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														ctt Leu		96	
														ttg Leu		144	
											-	-	-	cta Leu		192	
														gtc Val		240	
											_	-		ctc Leu 95		288	
														gta Val		336	
														gaa Glu		384	
tat	gat	tcc	ttt	tca	aat	cga	tgg	act	gaa	gtt	gct	ссс	ctt	aag	gaa	432	

Tyr	Asp 130		Phe	Ser	· Asn	Arg 135		Thr	Glu	ı Val	Ala 140		Leu	Lys	Glu	
	۷a٦		tct Ser			Val					Gly				gtg Val 160	480
			gga Gly		Asp											528
			gaa Glu 180													576
gcc Ala	aaa Lys	agg Arg 195	tgt Cys	ata Ile	aca Thr	gct Ala	gta Val 200	tcc Ser	cta Leu	aac Asn	aac Asn	ctg Leu 205	atc Ile	tat Tyr	gtt Val	624
gcc Ala	ggt Gly 210	gga Gly	ctg Leu	acc Thr	aag Lys	gca Ala 215	ata Ile	tac Tyr	tgt Cys	tac Tyr	gat Asp 220	cca Pro	gtt Val	gaa G1u	gat Asp	672
tac Tyr 225	tgg Trp	atg Met	cac His	gta Val	cag Gln 230	aat Asn	aca Thr	ttc Phe	agc Ser	cgt Arg 235	cag Gln	gaa Glu	aac Asn	tgt Cys	ggt Gly 240	720
atg Met	tct Ser	gtg Val	tgt Cys	aat Asn 245	ggt Gly	aaa Lys	ata Ile	tat Tyr	atc I1e 250	ctg Leu	ggc Gly	gga Gly	aga Arg	cgg Arg 255	gaa Glu	768
			gcc Ala 260													816
atc Ile	He	aca Thr 275	ggg Gly	gta Val	gct Ala	Ala	atg Met 280	ccc Pro	agg Arg	cca Pro	gtg Val	tcc Ser 285	tat Tyr	cat His	ggc Gly	864
Cys	gtg Val 290	act Thr	att Ile	cat His	Arg	tac Tyr 295	aat Asn	gag Glu	aaa Lys	Cys	ttt Phe 300	aaa Lys	ctc Leu	tga *		909

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Tyr Thr Glu Cys Tyr Asp Pro Val Thr Gly Glu Trp Lys Ser Leu Ala
Lys Leu Pro Glu Phe Thr Lys Ser Glu Tyr Ala Val Cys Ala Leu Arg
                        55
Asn Asp Ile Leu Val Ser Gly Gly Arg Ile Asn Ser Arg Asp Val Trp
Ile Tyr Asn Ser Gln Leu Asn Ile Trp Xaa Arg Val Ala Ser Leu Asn
                                    90
Lys Gly Arg Trp Arg His Lys Met Ala Val Leu Leu Gly Lys Val Tyr
            100
                                105
Val Val Gly Gly Tyr Asp Gly Gln Asn Arg Leu Ser Ser Val Glu Cys
                            120
                                                 125
Tyr Asp Ser Phe Ser Asn Arg Trp Thr Glu Val Ala Pro Leu Lys Glu
                        135
                                            140
Ala Val Ser Ser Pro Ala Val Thr Ser Cys Val Gly Lys Leu Phe Val
                    150
                                        155
Ile Gly Gly Pro Asp Asp Asn Thr Cys Ser Asp Lys Val Gln Ser
                165
                                    170
Tyr Asp Pro Glu Thr Asn Ser Trp Leu Leu Arg Ala Ala Ile Pro Ile
            180
                                185
Ala Lys Arg Cys Ile Thr Ala Val Ser Leu Asn Asn Leu Ile Tyr Val
        195
                            200
Ala Gly Gly Leu Thr Lys Ala Ile Tyr Cys Tyr Asp Pro Val Glu Asp
                        215
                                            220
Tyr Trp Met His Val Gln Asn Thr Phe Ser Arg Gln Glu Asn Cys Gly
                                        235
Met Ser Val Cys Asn Gly Lys Ile Tyr Ile Leu Gly Gly Arg Arg Glu
                                    250
Asn Gly Glu Ala Thr Asp Thr Ile Leu Cys Tyr Asp Pro Ala Thr Ser
```

		275		Val			280		Arg			285		Gly	
Cys	Va1 290		Ile	His	Arg	Tyr 295	Asn	Glu	Lys	Cys	Phe 300		Leu		
	<		405 DNA	o sa	pien	s									
	<;	220> 221> 222>		(4	405)										
	<	222>	(1)	c_fe (4 A,T	405)										
	ccg		cta				ctg Leu								48
							gta Val								96
							ggc Gly 40								144
							cca Pro								192
							gga Gly								240
							999 Gly								288

```
gca atg gct ttc cag gtc cca ccc aac tca ccc cag ggg agt gtg gcc
                                                                       336
Ala Met Ala Phe Gln Val Pro Pro Asn Ser Pro Gln Gly Ser Val Ala
             100
                                 105
                                                      110
tgc ccg ccc cct cca gcc tac tgc aac acg cct ccg ccc ccg tac gaa
                                                                       384
Cys Pro Pro Pro Pro Ala Tyr Cys Asn Thr Pro Pro Pro Pro Tyr Glu
        115
                             120
cag gta gtg aag gcc aag tag
                                                                       405
Gln Val Val Lys Ala Lys *
    130
      <210> 182
      <211> 134
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      <213> Homo sapiens
      <220>
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      <400> 182
Met Pro Leu Leu Arg Gly Leu Leu Trp Leu Gln Val Leu Cys Ala Gly
Pro Leu His Thr Glu Ala Val Val Leu Leu Val Pro Ser Asp Asp Gly
                                25
Arg Ala Phe Leu Leu Arg Xaa Gly Phe Phe Ile Arg Arg Arg Met Tyr
                            40
                                                 45
Pro Pro Pro Leu Ile Glu Glu Pro Ala Phe Asn Val Ser Tyr Thr Arg
Gln Pro Pro Asn Pro Gly Pro Gly Ala Gln Gln Pro Gly Pro Pro Tyr
                    70
                                         75
Tyr Thr Asp Pro Gly Gly Pro Gly Met Asn Pro Val Gly Asn Ser Met
Ala Met Ala Phe Gln Val Pro Pro Asn Ser Pro Gln Gly Ser Val Ala
                                105
Cys Pro Pro Pro Pro Ala Tyr Cys Asn Thr Pro Pro Pro Pro Tyr Glu
        115
                            120
                                                 125
Gln Val Val Lys Ala Lys
    130
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<210> 183

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	<	220> 221> 222>	CDS	(900)												
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	gag		gcg												gtc Val	48	
				Gly											cct Pro	96	
				gat Asp												144	
				cag Gln												192	
				atg Met												240	
				aga Arg 85					Lys	Gly	Ile		Phe			288	
gtc Val	aac Asn	agc Ser	gtg Val 100	gcg Ala	ctg Leu	aac Asn	999 Gly	gat Asp 105	ggc Gly	tgt Cys	ggc Gly	atc Ile	tgc Cys 110	tct Ser	gaa G1u	336	
				ctc Leu												384	

						cgg Arg 135	Cys					Leu					432
						cag G1n											480
						gac Asp											528
						gac Asp											576
						ccg Pro											624
						cac His 215										23	672
						aac Asn										•	720
						tac Tyr											768
gag Glu	gat Asp	gtg Val	gtt Val 260	ttg Leu	atc Ile	atc Ile	tac Tyr	tgt Cys 265	gga Gly	gtg Val	gtg Val	ggc Gly	ttc Phe 270	ctt Leu	gtg Val		816
gtc Val	Leu	aca Thr 275	ctc Leu	act Thr	cac His	ttt Phe	ggg G1 <i>y</i> 280	ctt Leu	cta Leu	gcc Ala	tca Ser	cct Pro 285	ttt Phe	ctt Leu	tct Ser		864
Gly						aag Lys 295					tga *						900

<210> 184

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       <223> Xaa = Any Amino Acid
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Val Phe Ile Leu Gly Asp Ile Phe Asp Glu Gly Lys Trp Ser Thr Pro
                                 25
Xaa Ala Trp Ala Asp Asp Val Glu Arg Phe Gln Lys Met Phe Arg His
                            40
Pro Ser His Val Gln Leu Lys Val Val Ala Gly Asn His Asp Ile Gly
Phe His Tyr Glu Met Asn Thr Tyr Lys Val Glu Arg Phe Glu Lys Val
                    70
                                        75
Phe Ser Ser Glu Arg Leu Phe Ser Trp Lys Gly Ile Asn Phe Val Met
Val Asn Ser Val Ala Leu Asn Gly Asp Gly Cys Gly Ile Cys Ser Glu
            100
                                105
Thr Glu Ala Glu Leu Ile Glu Val Ser His Arg Leu Asn Cys Ser Arg
                            120
Glu Ala Arg Gly Ser Ser Arg Cys Gly Pro Gly Pro Leu Leu Pro Thr
                        135
Ser Ala Pro Val Leu Leu Gln His Tyr Pro Leu Tyr Arg Arg Ser Asp
                    150
                                        155
Ala Asn Cys Ser Gly Glu Asp Ala Ala Pro Ala Glu Glu Arg Asp Ile
                165
                                    170
Pro Phe Lys Glu Asn Tyr Asp Val Leu Ser Arg Glu Ala Ser Gln Lys
                                185
Leu Leu Trp Trp Leu Gln Pro Arg Leu Val Leu Ser Gly His Thr His
                            200
                                                205
Ser Ala Cys Glu Val His His Gly Gly Arg Val Pro Glu Leu Ser Val
                        215
Pro Ser Phe Ser Trp Arg Asn Arg Asn Pro Ser Phe Ile Met Gly
                    230
                                        235
Ser Ile Thr Pro Thr Asp Tyr Thr Leu Ser Lys Cys Tyr Leu Pro Arg
```

				0.45	•				000						_	
G1u	ı Asp	Val	Val 260			e Ile	Tyr	Cys 265			Val	Gly	•		ı Val	
۷a۱	Leu	Thr 275	` Leu		His	Phe	Gly 280	Leu		ı Ala	a Ser	Pro 285			ı Ser	
Gly	Leu 290	ı Asr		ı Leu	ı Gly	Lys 295	Arg		Thr	Arg	I	200				
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		220>														
			CDS (1)		453)							,				
			185						*							
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cct	act	gaa	tca	ctc	ttc	tat	cgt	gct	gtt	ctt	cag	gat	att	att	aaa	96
Pro	Thr	Glu	Ser 20	Leu	Phe	Tyr	Arg	Ala 25	Val	Leu	Gln	Asp	Ile 30	Пе	Lys	
						aaa Lys										144
tcc Ser	aaa Lys 50	tgt Cys	tct Ser	tct Ser	ttt Phe	ctg Leu 55	gat Asp	tat Tyr	gtc Val	aga Arg	cgg Arg 60	tct Ser	cta Leu	aag Lys	aag Lys	192
ctt Leu 65	gga Gly	tta Leu	gat Asp	gag Glu	tcc Ser 70	aag Lys	ctg Leu	cca Pro	gaa Glu	aaa Lys 75	att Ile	ata Ile	atg Met	aac Asn	tac Tyr 80	240
tac Tyr	gag Glu	aag Lys	tat Tyr	aag Lys 85	cct Pro	cga Arg	atg Met	aat Asn	gag Glu 90	ctg Leu	gaa Glu	gct Ala	ttt Phe	aat Asn 95	atg Met	288
ttg Leu	aaa Lys	gtt Val	gta Val	ctg Leu	gct Ala	ccc Pro	tgt Cys	ata Ile	gag Glu	act Thr	ttg Leu	att Ile	ctt Leu	ctg Leu	gat Asp	336

<211> 1491

263

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			DNA Hom	o sa	pier	ıs										
	<		CDS	(1491)										
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gtg Val	ggc Gly	tgc Cys	gtc Val 20	ttc Phe	ctg Leu	ctg Leu	gag Glu	cca Pro 25	Glu	ctg Leu	cca Pro	ggc Gly	tcg Ser 30	Ala	ctg Leu	96
														ccc Pro		144
gga Gly	ccc Pro 50	gtc Val	tcc Ser	ccc Pro	gag Glu	ggc Gly 55	cgg Arg	ttg Leu	gcg Ala	gca Ala	gcc Ala 60	tgg Trp	gac Asp	gcg Ala	ctt Leu	192
											A1 a			gtc Val		240
gca Ala	tgt Cys	gtt Val	gat Asp	gtg Val 85	gtg Val	ctc Leu	tca Ser	ggg Gly	gtg Val 90	aag Lys	ctc Leu	ttg Leu	cag G1n	gca Ala 95	ctt Leu	288
														tca Ser		336
														gca Ala		384
41a														gcc Ala		432

	Ala					Gly					Val	gga Gly			gca Ala 160	480
					Lys							tta Leu			Leu	528
									His			ctt Leu				576
gtc Val	ttt Phe	gtt Val 195	cca Pro	cca Pro	gag Glu	tca Ser	ttg Leu 200	cag Gln	gaa Glu	gtg Val	gat Asp	gag Glu 205	ttc Phe	cac His	ctc Leu	624
att Ile	tta Leu 210	gag Glu	tat Tyr	caa G1n	gca Ala	999 Gly 215	gag G1u	gag Glu	tgg Trp	ggc Gly	cag Gln 220	tta Leu	aaa Lys	gct Ala	ccc Pro	672
												aac Asn				720
aat Asn	atg Met	ctg Leu	gag Glu	gtg Val 245	ttt Phe	gtg Val	tct Ser	agc Ser	ctg Leu 250	gag Glu	gag Glu	ttt Phe	cag Gln	cca Pro 255	gac Asp	768
ctg Leu	gtg Val	gtc Val	ctc Leu 260	tct Ser	gga Gly	ttg Leu	cac His	atg Met 265	atg Met	gag Glu	gga Gly	caa Gln	agc Ser 270	aag Lys	gag Glu	816
	Gln					Leu						att Ile 285				864
ro					Val					Ala		atg Met				912
				Ser					Val			gcg Ala		Thr		960

						acc Thr					1008
						gtt Val		-			1056
		Asp				gaa Glu				-	1104
						tto Phe 380					1152
						gcc Ala					1200
						cag Gln	-	-	-		1248
				-	_	 gca Ala					1296
						gta Val					1344
						tcc Ser 460					1392
						gta Val					1440
		Ala			_	 gta Val					1488

tag

267

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Leu Val Val Leu Ser Gly Leu His Met Met Glu Gly Gln Ser Lys Glu

Lou			260					265					070		
10			• •					265					270)	
LCI	ı Gin	Arg 275		Arg	Leu	Leu	G1u 280		Val	Thr	Ser	Ile 285		Asp	Ile
Pro	7hr 290	Gly	Ile	Pro	۷a٦	His 295		Glu	Leu	Ala	Ser 300	Met		Asn	Arg
G1u 309	ı Leu	Met	Ser	Ser	Ile 310	Val		Gln	Val	Phe 315	Pro		۷a٦	Thr	Ser 320
	Gly	Leu	Asn	G1u 325			Leu	Leu	Phe 330			Gln	Ser	Ala 335	Ser
Gly	/ Pro	His	Ser 340		Leu	Ser	Ser	Trp 345		Gly	Val	Pro	Asp 350	Val	
Met	: Val	Ser 355	Asp	Пe	Leu	Phe	Trp 360		Leu	Lys	Glu	His 365			Ser
Lys	Ser 370			Ser	Asp	Leu 375		Arg	He	His	Phe 380		Thr	Leu	۷al
385					390					395	Ala				400
	Val			405					410					415	Thr
	Thr		420					425					430		
	Thr	435					440					445			
	Pro 450					455					460				
465					470					475				•	480
Ala	Ile	Ser	Ala	G1u 485	Gly	Leu	Phe	Tyr	Ser 490	Glu	Val	His	Pro	His 495	Tyr
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					gcg Ala			ccc Pro		96
					ctg Leu				1	.44
					atg Met				1	92
					atg Met 75				2	40
					ctc Leu				2	88
					aag Lys				3:	36
tga *									33	39

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<213> Homo sapiens

<400> 190

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 Pro Gly Thr Ala Ala Ala Ala Pro Ala Lys Pro Ala Pro Pro Ala Thr Pro 20
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 30
 30

 Gly Ala Pro Thr Ser Pro Ala Glu His Arg Leu Leu Lys Thr Cys Trp 35
 40
 45

 Ser Cys Arg Val Leu Ser Gly Leu Gly Leu Met Gly Ala Gly Gly Tyr 50
 55
 60

 Val Tyr Trp Val Ala Arg Lys Pro Met Lys Met Gly Tyr Pro Pro Ser

65 Pro	Trp) Thr	· Ile	e Thr	70 Glr	n Met	: Val	l Ile	e G1v	75 / Lei	ı Ser	· Ile	e Ala	n Thr	80 Trp	
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Met 1	Ala	Ala	Ala	Met 5	Ala	Ala	Ser	Ser	Leu 10	Thr	Val	Thr	Leu	999 Gly 15	Arg	48
ctg Leu	gcg Ala	tcc Ser	gcg Ala 20	tgc Cys	agc Ser	cac His	agc Ser	atc Ile 25	ctg Leu	aga Arg	cct Pro	tcg Ser	999 Gly 30	ccc Pro	gga Gly	96
gca Ala	gcc Ala	tcc Ser 35	ctt Leu	tgg Trp	tct Ser	gct Ala	tct Ser 40	cga Arg	agg Arg	ttc Phe	aat Asn	tca Ser 45	cag G1n	agc Ser	act Thr	144
tca Ser	tat Tyr 50	cta Leu	cca Pro	gga Gly	tat Tyr	gtt Val 55	cct Pro	aaa Lys	aca Thr	tcc Ser	ctg Leu 60	agt Ser	tca Ser	cca Pro	cct Pro	192
tgg Trp 65	cca Pro	gaa Glu	gtt Val	gtt Val	ctg Leu 70	cca Pro	gac Asp	cca Pro	gtt Val	gag Glu 75	gag Glu	acc Thr	aga Arg	cac His	cat His 80	240
gca Na	gag G1u	gtc Val	gtg Val	aag Lys 85	aag Lys	gtg Val	aat Asn	gag Glu	atg Met 90	atc Ile	gtc Val	acg Thr	999 Gly	cag Gln 95	tat Tyr	288
ggc Gly	agg Arg	ctc Leu	ttt Phe 100	gcc Ala	gtg Val	gtg Val	cac His	ttt Phe 105	gcc Ala	agc Ser	cgc Arg	cag Gln	tgg Trp 110	aag Lys	gtg Val	336

acc Thr	tct Ser	gaa Glu 115	Asp	ctg Leu	atc Ile	tta Leu	att Ile 120	gga Gly	aat Asn	gaa Glu	cta Leu	gac Asp 125	Leu	gcg Ala	tgt Cys		384
	gag Glu 130																432
ttc Phe 145	acg Thr	ctg Leu	ctt Leu	ggc Gly	aag Lys 150	cca Pro	ctc Leu	ctc Leu	gga Gly	aag Lys 155	gat Asp	ctt Leu	gtt Val	cga Arg	gta Val 160	•	480
gaa Glu	gcc Ala	aca Thr	gtc Val	att Ile 165	gaa Glu	aag Lys	aca Thr	gaa G1u	tca Ser 170	tgg Trp	cca Pro	aga Arg	atc Ile	att Ile 175	atg Met	ţ	528
aga Arg	ttc Phe	agg Arg	aaa Lys 180	agg Arg	aaa Lys	aac Asn	ttc Phe	aag Lys 185	aag Lys	aaa Lys	aga Arg	atc Ile	gtc Val 190	acg Thr	acc Thr		576
ccg Pro	cag G1n	act Thr 195	gtc Val	ctc Leu	cgg Arg	He	aac Asn 200	agc Ser	att Ile	gag Glu	att Ile	gct A1a 205	ccg Pro	tgt Cys	ttg Leu	6	524
ttg _eu	tga *															6	30

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<213> Homo sapiens

<400> 192

 Met
 Ala
 Ala
 Met
 Ala
 Ala
 Ala
 Ala
 Ala
 Ser
 Leu
 Thr
 Val
 Thr
 Leu
 Gly
 Arg

 Leu
 Ala
 Ser
 Ala
 Cys
 Ser
 His
 Ser
 Ile
 Leu
 Arg
 Pro
 Ser
 Gly
 Pro
 Gly
 Pro
 Gly
 Arg
 Pro
 Ser
 Gly
 Pro
 Fro
 Pro
 P

	65					70					75					80	
	Ala	G1ı	ı Val	Val	Lys 85	Lys	: Val	Asr	G1u	Met 90	: Ile	e Val	Thr	. G17	G1r 95	ı Tyr	
	Gly	Arg	l Leu	Phe 100		Va1	Val	His	Phe 105		Ser	· Arg	Glr	Trp 110	Lys	Val	
			115	•				120					125	•		Cys	
		130					135					140			•	Asn	
	145					150					155					Val 160	
	Glu	Ala	Thr	· Val	Ile 165		Lys	Thr	Glu	Ser 170	Trp	Pro	Arg	He	11e 175	Met	
				180					185					190		Thr	
	Pro	Gln	Thr 195		Leu	Arg	Ile	Asn 200	Ser	Ile	Glu	Ile	A1a 205		Cys	Leu	
	Leu																
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												ccc Pro					96
Ģ	ga Ny	gcg Ala	ccg Pro 35	acc Thr	tcc Ser	cca Pro	gca Ala	gaa Glu 40	cac His	cgc Arg	ctg Leu	ttg Leu	aag Lys 45	acc Thr	tgc Cys	tgg Trp	144
S	igc ier	tgt Cys	cgc Arg	gtg Val	ctt Leu	tct Ser	999 Gly	ttg Leu	999 Gly	ctg Leu	atg Met	999 Gly	gcg Ala	ggc Gly	999 Gly	tac Tyr	192

	5()				55	•				60)				
gtg Val 65	Tyr	tg: Tr	g gtg Val	gca Ala	cgg Arg 70	Lys	occ Pro	atg Met	aag Lys	atg Met 75	: G1y	a tad ⁄Tyr	c ccc Pro	c ccç Pro	agt Ser 80	240
cca Pro	tgg Trp	aco Thr	att Ile	acg Thr 85	Gln	atg Met	gto Val	atc Ile	ggc Gly 90	Leu	agt Ser	gag Glu	aat Asr	caa Glr 95	ggc Gly	288
att Ile	gcc	acc Thr	tgg Trp 100	Gly	atc Ile	gtt Val	gtc Val	atg Met 105	Ala	gac Asp	ccc Pro	aaa Lys	999 Gly	' Lys	gcc Ala	336
			gtt Val	tga *												351
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Met 1			194 Arg	Leu 5	Ser	Gìn	Pro	Phe	Glu 10	Ser	Tyr	Ile	Thr	Ala 15	Pro	
			A1a 20					25	Pro				30	Thr		
Gly	Ala	Pro 35	Thr	Ser	Pro		G1u 40	His	Arg	Leu	Leu	Lys 45	Thr	Cys	Trp	
Ser	Cys 50	Arg	Val	Leu		Gly 55	Leu	Gly	Leu		Gly 60	Ala	Gly	Gly	Tyr	
Val 65	Tyr	Trp	Val		Arg 70	Lys	Pro	Met	Lys	Met 75	Gly	Tyr	Pro	Pro	Ser 80	
Pro	Trp	Thr	Ile			Met	Val	Ile	G1 <i>y</i> 90	Leu	Ser	Glu	Asn	G]n 95	Gly	
	Ala Arg		Trp 100		Ile	Val				Asp	Pro	Lys	Gly 110	Lys	Ala	
		10> 11>	195 1047													

			> DNA > Hor		apier	าร										
	<		> > CDS > (1)		1047	')										
atç Met 1	g cgg	cto	→ 195 ctc Leu	ggc	tgg Trp	ı tgg Trp	caa Gln	gta Val	ttg Leu 10	ı Let	ı tgç ı Trp	g gtg o Val	ctg Leu	gga Gly 15	ctt Leu	48
ccc Pro	gto Val	cgc Arg	ggc Gly 20	Val	gag Glu	gtt Val	gca Ala	gag Glu 25	Glu	agt Ser	ggt Gly	cgc Arg	tta Leu 30	Trp	tca Ser	96
gag Glu	gag Glu	cag Gln 35	cct Pro	gct Ala	cac His	cct Pro	ctc Leu 40	Gln	gtg Val	999 Gly	gct Ala	gtg Val 45	Tyr	ctg Leu	ggt Gly	144
gag Glu	gag Glu 50	gag Glu	ctc Leu	ctg Leu	cat His	gac Asp 55	ccg Pro	atg Met	ggc Gly	cag Gln	gac Asp 60	Arg	gca Ala	gca Ala	gaa Glu	192
gag Glu 65	Ala	aat Asn	gcg Ala	gtg Val	ctg Leu 70	ggg Gly	ctg Leu	gac Asp	acc Thr	caa Gln 75	ggc Gly	gat Asp	cac His	atg Met	gtg Val 80	240
atg Met	ctg Leu	tct Ser	gtg Val	att Ile 85	cct Pro	999 Gly	gaa Glu	gct Ala	gag Glu 90	gac Asp	aaa Lys	gtg Val	agt Ser	tca Ser 95	gag Glu	288
cct Pro	agc Ser	ggc Gly	gtc Val 100	acc Thr	tgt Cys	ggt Gly	gct Ala	gga Gly 105	gga Gly	gcg Ala	gag Glu	gac Asp	tca Ser 110	agg Arg	tgc Cys	336
aac Asn	gtc Val	cga Arg 115	gag Glu	agc Ser	ctt Leu	ttc Phe	tct Ser 120	ctg Leu	gat Asp	ggc Gly	gct Ala	gga Gly 125	gca Ala	cac His	ttc Phe	384
cct Pro	gac Asp 130	aga Arg	gaa Glu	gag G1u	Glu	tat Tyr 135	tac Tyr	aca Thr	gag Glu	cca Pro	gaa Glu 140	gtg Val	gcg Ala	gaa Glu	tct Ser	432

	Ala					Asp					Glu				tcc Ser 160		480
					Glu					Thr					ttc Phe		528
act Thr	ctg Leu	aaa Lys	att Ile 180	Leu	aat Asn	atg Met	tca Ser	cag Gln 185	gac Asp	ctt Leu	atg Met	gat Asp	ttt Phe 190	ctg Leu	aac Asn		576
			Ser			act Thr							Pro			ı	624
						gcc Ala 215										=	672
ttt Phe 225	cca Pro	gct Ala	ctt Leu	cac His	ttt Phe 230	ttg Leu	gca Ala	ctg Leu	gat Asp	gca Ala 235	tct Ser	cag Gln	cac His	agc Ser	agc Ser 240		720
ctt Leu	tct Ser	acc Thr	agg Arg	ttt Phe 245	ggc Gly	acc Thr	gta Val	gct Ala	gtt Val 250	cct Pro	aat Asn	att Ile	tta Leu	tta Leu 255	ttt Phe	7	768
						gcc Ala									ctg Leu ု	3	316
gaa Glu	aca Thr	ctg Leu 275	aaa Lys	atc Ile	ttc Phe	att Ile	ttt Phe 280	aat Asn	cag Gln	aca Thr	ggt Gly	ata Ile 285	gaa Glu	gcc Ala	aag Lys	8	364
Lys	aat Asn 290	gtg Val	gtg Val	gta Val	Thr	caa G1n 295	gcc Ala	gac Asp	caa G1n	ata Ile	ggc Gly 300	cct Pro	ctt Leu	ccc Pro	agc Ser	9	12
				Ser		gac Asp			Leu					Phe		9	160

tta att agt ttt att atg tat gct acc att cga act gag agt att cgg 1008 Leu Ile Ser Phe Ile Met Tyr Ala Thr Ile Arg Thr Glu Ser Ile Arg 325 330 335 tgg cta att cca gga caa gag cag gaa cat gtg gag tag 1047 Trp Leu Ile Pro Gly Gln Glu Gln Glu His Val Glu * 340 <210> 196 <211> 348 <212> PRT <213> Homo sapiens <400> 196 Met Arg Leu Leu Gly Trp Trp Gln Val Leu Leu Trp Val Leu Gly Leu 10 Pro Val Arg Gly Val Glu Val Ala Glu Glu Ser Gly Arg Leu Trp Ser Glu Glu Gln Pro Ala His Pro Leu Gln Val Gly Ala Val Tyr Leu Gly Glu Glu Leu Leu His Asp Pro Met Gly Gln Asp Arg Ala Ala Glu 55 Glu Ala Asn Ala Val Leu Gly Leu Asp Thr Gln Gly Asp His Met Val Met Leu Ser Val Ile Pro Gly Glu Ala Glu Asp Lys Val Ser Ser Glu Pro Ser Gly Val Thr Cys Gly Ala Gly Gly Ala Glu Asp Ser Arg Cys 105 Asn Val Arg Glu Ser Leu Phe Ser Leu Asp Gly Ala Gly Ala His Phe 120 Pro Asp Arg Glu Glu Glu Tyr Tyr Thr Glu Pro Glu Val Ala Glu Ser 135 140 Asp Ala Ala Pro Thr Glu Asp Ser Asn Asn Thr Glu Ser Leu Lys Ser 155 Pro Lys Val Asn Cys Glu Glu Arg Asn Ile Thr Gly Leu Glu Asn Phe 165 170 Thr Leu Lys Ile Leu Asn Met Ser Gln Asp Leu Met Asp Phe Leu Asn 185 Pro Asn Gly Ser Asp Cys Thr Leu Val Leu Phe Tyr Thr Pro Trp Cys

Arg Phe Ser Ala Ser Leu Ala Pro His Phe Asn Ser Leu Pro Arg Ala

Phe Pro Ala Leu His Phe Leu Ala Leu Asp Ala Ser Gln His Ser Ser

220

225	5				230)				235	5				240	
Let	ı Ser	Thr	· Arç	9 Phe 245		/ Thr	· Val	Ala	Val 250	Pro		ı Ile	Lei	ب Lei 255	ı Phe	
Glr	n Gly	' A1a	1 Lys 260		Met	: Ala	Arg	Phe 265		His	Thr	· Asp	270 270	7 Thr	Leu	
		275	;)				280)				285)		a Lys	
	290					295					300	ł) Ser	
305	•				310)				315					Phe 320	
				325					330				Ser	335 335	e Arg	
Trp	Leu	Ile	Pro 340		Gln	G7u	Gln	G1u 345		Val	Glu					
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acg Thr	cca Pro	atg Met	act Thr 20	gag Glu	aat Asn	gga Gly	gaa G1u	atc Ile 25	aac Asn	ttt Phe	tca Ser	gta Val	att Ile 30	ggt Gly	cag Gln	96
tat Tyr	gtg Val	gat Asp 35	tat Tyr	ctt Leu	gtg Val	aaa Lys	gaa G1u 40	cag Gln	gga Gly	gtg Val	aag Lys	aac Asn 45	att Ile	ttt Phe	gtg Val	144
aat Asn	ggc Gly 50	aca Thr	aca Thr	gga Gly	gaa Glu	ggc Gly 55	ctg Leu	tcc Ser	ctg Leu	agc Ser	gtc Val 60	tca Ser	gag Glu	cgt Arg	cgc Arg	192
ag In	gtt Val	gca Ala	gag Glu	gag Glu	tgg Trp	gtg Val	aca Thr	aaa Lys	999 Gly	aag Lys	gac Asp	aag Lys	ctg Leu	gat Asp	cag Gln	240

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					Gly					Lys					ctg Leu	288
gcc Ala	caa G1n	cat His	gca Ala 100	Ala	gaa Glu	ata Ile	gga Gly	gct Ala 105	Asp	ggc Gly	ato Ile	gct Ala	gtc Val	Пe	gca Ala	336
ccg Pro	ttc Phe	ttc Phe 115	Leu	aag Lys	cca Pro	tgg Trp	acc Thr 120	Lys	gat Asp	atc Ile	ctg Leu	att Ile 125	Asn	ttc Phe	cta Leu	384
												att Ile				432
	ctg Leu		tga *													444
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Thr	Pro	Met	Thr 20	Glu	Asn	Gly	Glu	Ile 25	Asn	Phe	Ser	Val	Ile 30	Gly	Gln	
Tyr	Va1	Asp 35		Leu	Val		G1u 40		G1y	Val	Lys	Asn		Phe	Val	
Asn	Gly 50		Thr	Gly	Glu			Ser	Leu	Ser	Va1 60	45 Ser	Glu	Arg	Arg	,
G1n 55		Ala	Glu	Glu	Trp 70		Thr	Lys	Gly	Lys 75		Lys	Leu	Asp	G1n 80	
	Пe	Пe		Va1 85		Аlа	Leu	Ser	Leu 90		Glu	Ser	Gln	G1u 95		
47a	Gln	His			Glu	Пе	Gly	A7a 105		Gly	Ile	Ala	Val 110		Ala	
ro	Phe	Phe		Lys	Pro	Trp	Thr		Asp	Ile	Leu	Ile		Phe	Leu	

	130 Leu		A1a	ı Ala	ı Ala	Pro 135			Cys	His	: Phe 140			. Ile	· Thr	
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						cat His										144
						att Ile 55										192
						gtc Val										240
aaa _ys	tgg Trp	gct Ala	ggt Gly	ggt Gly 85	gga Gly	ttt Phe	ctg Leu	tct Ser	aca Thr 90	gtg Val	ggt Gly	gac Asp	ctt Leu	ctg Leu 95	aaa Lys	288

												aag Lys		336
												atg Met		384
												aaa Lys		432
									-			acg Thr		480
												999 Gly 175		528
 	-	-	-	-	-	_			~	•	_	gat Asp		576
											-	tct Ser		624
_		_			-			-		-	-	aag Lys		672
ctt Leu								tga *						705

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												tcc Ser				96
												gac Asp 45				144
								_		-		ccc Pro		_	_	192
												gag Glu				240
												gta Val				288
												gac Asp				336
												gtc Val 125				384
Val												gtt Val				432
cca Pro 145	ttt Phe	tcc Ser	gaa Glu	Tyr	aca Thr 150	gct Ala	tgg Trp	gca Ala	Met	gta Val 155	gat Asp	ggt Gly	ggt Gly	tca Ser	aat Asn 160	480

gtg Val	aaa Lys	gcc Ala	cgc Arg	tct Ser 165	Ser	tac Tyr	aat Asn	gag Glu	aag Lys 170	acc Thr	cca Pro	agg Arg	ntc Xaa	gtt Val 175	gtg Val	5	528
											gct Ala					5	76
gga Gly	aac Asn	cag Gln 195	act Thr	aca Thr	att Ile	atc Ile	cca Pro 200	gct Ala	ggt Gly	ggt Gly	gct Ala	ggt G1y 205	tat Tyr	aaa Lys	gtt Val	6	24
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											ata Ile					7:	20
											acc Thr					76	68
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						Gln					aaa Lys					86	64
Glu				cat His		tga *										88	35

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				Gln					Pro						agc Ser	96
cat His	ctc Leu	cac His 35	Gln	aag Lys	cct Pro	ggc Gly	cag Gln 40	Thr	tgg Trp	aag Lys	aac Asn	aaa Lys 45	gag Glu	cat His	cat His	144
									gaa Glu							192
aga Arg 65	gct Ala	cct Pro	gag Glu	cca Pro	cga Arg 70	gtg Val	att Ile	gac Asp	aga Arg	gag Glu 75	ggt Gly	gtg Val	tat Tyr	gaa Glu	atc Ile 80	240
agc Ser	ctg Leu	tca Ser	ccc Pro	aca Thr 85	ggt Gly	gta Val	tct Ser	agg Arg	gtc Val 90	tgt Cys	ttg Leu	tat Tyr	cct Pro	ggc Gly 95	ttt Phe	288
									ttg Leu							336
gtt Val	ccc Pro	tgg Trp 115	aaa Lys	cag Gln	agg Arg	acc Thr	ggc Gly 120	atc Ile	aga Arg	gag G1u	gat Asp	ata Ile 125	act Thr	tat Tyr	cag Gln	384
caa G1n	cca Pro	aga Arg	ctt Leu	aca Thr	gca Ala	tgg Trp	tat Tyr	gga Gly	gaa Glu	ctt Leu	cct Pro	tac Tyr	act Thr	tat Tyr	tca Ser	432

	130				135					140					
-		-	_		aat Asn							_	_		480
	-	_		_	gag Glu										528
	-			_	aat Asn			-	-		-			~	576
					999 Gly						-			_	624
					ttt Phe 215										672
		_			tat Tyr		_	_		-			_	-	720
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					tac Tyr										816
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<211> 286

<212> PRT

<213> Homo sapiens

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His	Leu	His 35	G1n	Lys	Pro	Gly	G1n 40	Thr	Trp	Lys	Asn	Lys 45	Glu	His	His
Leu	Ser 50	Asp	Arg	Glu	Phe	Va1 55	Phe	Lys	G1u	Pro	G1n 60	Gln	Val	Val	Arg
65					70					G1u 75					80
Ser	Leu	Ser	Pro	Thr 85	Gly	Val	Ser	Arg	Va1 90	Cys	Leu	Tyr	Pro	Gly 95	Phe
			100					105		Glu			110		·
		115					120			Glu		125		_	
	130					135				Leu	140				
Arg 145	Ile	Thr	Met	Glu	Pro 150	Asn	Pro	His	Trp	His 155	Pro	Val	Leu	Arg	Thr 160
Leu	Lys	Asn	Arg	Ile 165	Glu	Glu	Asn	Thr	Gly 170	His	Thr	Phe	Asn	Ser 175	Leu
Leu	Cys	Asn	Leu 180	Tyr	Arg	Asn	Glu	Lys 185	Asp	Ser	۷al	Asp	Trp 190	His	Ser
		195					200			Ile		205			
Phe	Gly 210	Ala	Thr	Arg	Thr	Phe 215	Glu	Met	Arg	Lys	Lys 220	Pro	Pro	Pro	Glu
G1u 225	Asn	Gly	Asp	Tyr	Thr 230	Tyr	Val	Glu	Arg	Va1 235	Lys	Пе	Pro	Leu	Asp 240
His	Gly	Thr	Leu	Leu 245	Пe	Met	Glu	Gly	Ala 250	Thr	G1n	Ala	Asp	Trp 255	Gln
His	Arg	Val	Pro 260	Lys	G1u	Tyr	His	Ser 265	Arg	Glu	Pro	Arg	Val 270	Asn	Leu
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<211> 561

<212> DNA

<213> Homo sapiens

<220>

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cag gtg ctc cct gtg ttg aaa gag aat gtg gaa ggt cat gat tta cct 528 Gln Val Leu Pro Val Leu Lys Glu Asn Val Glu Gly His Asp Leu Pro 165 170 gca tct gag aaa cac cag gat gtt acc tcc taa 561 Ala Ser Glu Lys His Gln Asp Val Thr Ser * 180 <210> 206 <211> 186 <212> PRT <213> Homo sapiens <400> 206 Met Ile His Trp His Ser Glu Lys Ala Thr Leu Leu Leu Asn Ala Pro 10 Ser Phe Ser Asp Gln Leu Pro Gly Thr Met Ala Thr Leu Ser Leu Val 25 Asn Glu Ala Gln Tyr Leu Leu Ile Asn Thr Ser Ser Ile Leu Glu Leu His Arg Gln Leu Asn Thr Ser Asp Glu Asn Gly Lys Glu Glu Leu Phe Ser Leu Lys Asp Leu Ser Leu Arg Phe Arg Ala Asn Ile Ile Ile Asn Gly Lys Arg Ala Phe Glu Glu Glu Lys Trp Asp Glu Ile Ser Ile Gly Ser Leu Arg Phe Gln Val Leu Gly Pro Cys His Arg Cys Gln Met Ile 105 Cys Ile Asp Gln Gln Thr Gly Gln Arg Asn Gln His Val Phe Gln Lys 120 Leu Ser Glu Ser Arg Glu Thr Lys Val Asn Phe Gly Met Tyr Leu Met 135 140 His Ala Ser Leu Asp Leu Ser Ser Pro Cys Phe Leu Ser Val Gly Ser 150 155 Gln Val Leu Pro Val Leu Lys Glu Asn Val Glu Gly His Asp Leu Pro 165 170 Ala Ser Glu Lys His Gln Asp Val Thr Ser 180 185 <210> 207 <211> 1272 <212> DNA <213> Homo sapiens

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				Val					Tyr					Ā٦a	gat Asp	96
ttt Phe	tca Ser	ggc Gly 35	Pro	atg Met	atg Met	atc Ile	att Ile 40	act Thr	cag Gln	aag Lys	atc Ile	act Thr 45	agt Ser	ttg Leu	gct Ala	144
								cgg Arg								192
								cgc Arg								240
ttg Leu	agt Šer	tac Tyr	aac Asn	tgt Cys 85	aac Asn	ttc Phe	atg Met	999 Gly	atc Ile 90	ctg Leu	gca Ala	ngc Xaa	cca Pro	ntt Xaa 95	tgc Cys	288
		Lys		Tyr				att Ile 105								336
								gaa Glu								384
								gtt Val								432

	130					135	i				140					
	Ser					Leu					Thr				gag Glu 160	480
					His							tgg Trp			Lys	528
				Tyr					Ala			ccc Pro				576
			Thr					He				gca Ala 205				624
												gac Asp				672
												ttc Phe				720
												aaa Lys				768
												ttc Phe				816
												acg Thr 285				864
ggg Gly	gtg Val 290	tta Leu	atg Met	aca Thr	tta Leu	gca Ala 295	gca Ala	aga Arg	gct Ala	atg Met	aga Arg 300	aat Asn	aac Asn	ttt Phe	aga Arg	912
cat His	tat Tyr	ttc Phe	att Ile	gaa Glu	cct Pro	tcc Ser	caa Gln	ctg Leu	aaa Lys	tta Leu	ttt Phe	tat Tyr	gat Asp	gtt Val	ata Ile	960

PCT/US00/29052

305	310	315	320
Thr Trp Ile Val	act caa gta gca ato Thr Gln Val Ala Ilo 325	a agt tac aca gtt gtg e Ser Tyr Thr Val Val 330	cca ttt 1008 Pro Phe 335
		acg ttt tac agc tcc Thr Phe Tyr Ser Ser 350	
tat tgc ctg cac a Tyr Cys Leu His 1 355	att ctt ggt atc tta Ile Leu Gly Ile Leu 360	n gta tta ttg ttg ttg n Val Leu Leu Leu 365	cca gtg 1104 Pro Val
		cat gaa aac att cag His Glu Asn Ile Gln 380	
caa tcc aaa aag t G1n Ser Lys Lys F 385	ttt gat gaa gga gaa Phe Asp Glu Gly Glu 390	aat tct ttg gga cag Asn Ser Leu Gly Gln 395	aac agt 1200 Asn Ser 400
Phe Ser Thr Thr A		cag aat caa gaa ata Gln Asn Gln Glu Ile 410	
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Phe	Ser	Gly 35	Pro	Met	Met	Ile	Ile 40	Thr	Gln	Lys	Ile	Thr 45	Ser	Leu	Ala
	50				Gly	55				·	60				
65			-		Ala 70					75					80
Leu	Ser	Tyr	Asn	Cys 85	Asn	Phe	Met	Gly	11e 90	Leu	Ala	Xaa	Pro	Xaa 95	Cys
٠			100		Пe			105		_	-		110		
		115			Asn		120					125			
	130				Thr	135					140			•	
Leu 145	Ser	Leu	Leu	Phe	His 150	Leu	Thr	Ile	Cys	Thr 155	Thr	Leu	Pro	Val	G1u 160
				165	His				170			•		175	
		-	180	-	Пe			185			•		190		Ū
		195			Ala		200					205	v		Ū
	210				Glu	215					220				
Asn 225	Leu	Arg	Ile	Gln	G1n 230	Ile	Glu	Met	Ser	Thr 235	Ser	Phe	Lys	Met	Phe 240
Leu	Asp	Asn	Trp	Asn 245	Ile	G1n	Thr	Ala	Leu 250	Trp	Leu	Lys	Arg	Val 255	Cys
Tyr	G1u	Arg	Thr 260	Ser	Phe	Ser	Pro	Thr 265	Ile	Gln	Thr	Phe	Ile 270	Leu	Ser
		275		_	Val		280	_	-	_		285			
Gly	Va1 290	Leu	Met	Thr	Leu	A1a 295	Ala	Arg	Ala	Met	Arg 300	Asn	Asn	Phe	Arg
His 305	Tyr	Phe	Пе	Glu	Pro 310	Ser	Gln	Leu	Lys	Leu 315	Phe	Tyr	Asp	Val	Ile 320
Thr	Trp	Пe	Val	Thr 325	Gln	Val	Ala	Ile	Ser 330	Tyr	Thr	Val	Val	Pro 335	Phe
Val	Leu	Leu	Ser 340	Пе	Lys	Pro	Ser	Leu 345	Thr	Phe	Tyr	Ser	Ser 350		Tyr
Tyr	Cys	Leu 355	His	Ile	Leu	Gly	Ile 360	Leu	Val	Leu	Leu	Leu 365	Leu	Pro	Val

Lys	Lys 370		Gln	Arg	Arg	Lys 375		Thr	His	Glu	Asn 380		Gln	Leu	Ser	
G1n 385	Ser		Lys	Phe	Asp 390		Gly	Glu	Asn	Ser 395	Leu		Gln	Asn	Ser 400	
Phe	Ser	Thr	Thr	Asn 405	Asn	Val	Cys	Asn	G1n 410		Gln	Glu	He	Ala 415	Ser	
Arg	His	Ser	Ser 420		Lys	G1n										
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	ctg Leu															96
	cga Arg															144
	tcc Ser 50															192
	ctg Leu															240
agc Ser	ctt Leu	cca Pro	cgg Arg	gaa Glu 85	gga Gly	cag Gln	gag Glu	aag Lys	gtg Val 90	ctg Leu	gac Asp	cgc Arg	ctg Leu	gac Asp 95	ttt Phe	288
gtg	ctg	acc	agc	ctt	gtg	gcg	ctg	cgg	cgg	gag	gtg	gag	gag	ctg	aga	336

Val	Leu	ı Thr	Ser 100		ı Val	Ala	Leu	Arg 105		ı Glu	ı Val	Glu	110		ı Arg	
agc Ser	agc Ser	ctg Leu 115	Arg	999 Gly	ctt Leu	gcg Ala	999 Gly 120	Glu	att Ile	gtt Val	ggg Gly	gag Glu 125	Va1	cga Arg	tgc Cys	384
cac His	atg Met 130	Glu	gag Glu	aac Asn	cag Gln	aga Arg 135	۷a٦	gct Ala	cgg Arg	cgg Arg	cga Arg 140	Arg	ttt Phe	ccg Pro	ttt Phe	432
	Arg										Ser			ttc Phe		480
gcc Ala	tcc Ser	tcg Ser	gga Gly	gcc Ala 165	acg Thr	ttc Phe	aca Thr	gat Asp	gct Ala 170	gag Glu	agt Ser	gaa Glu	999 Gly	ggt Gly 175	tac Tyr	528
aca Thr	aca Thr	gcc Ala	aat Asn 180	gcg Ala	gag Glu	tct Ser	gac Asp	aat Asn 185	gag Glu	cgg Arg	gac Asp	tct Ser	gac Asp 190	aaa Lys	gaa Glu	576
agt Ser	gag Glu	gac Asp 195	999 Gly	gaa Glu	gat Asp	gaa Glu	gtg Val 200	agc Ser	tgt Cys	gag Glu	act Thr	gtg Val 205	aag Lys	atg Met	999 Gly	624
														gcc Ala		672
agt Ser 225	gcc Ala	ctg Leu	gag Glu	gct Ala	gga Gly 230	ggt Gly	tcc Ser	tca Ser	ggc Gly	ttg Leu 235	gag Glu	gat Asp	gtg Val	ctg Leu	ccc Pro 240	720
ctc Leu	ctg Leu	cag Gln	cag G1n	gcc Ala 245	gac Asp	gag Glu	ctg Leu	His	agg Arg 250	ggt Gly	gat Asp	gag Glu	caa G1n	ggc Gly 255	aag Lys	768
cgg Arg	gag Glu	Gly	ttc Phe 260	cag G1n	ctg Leu	ctg Leu	Leu	aac Asn 265	aac Asn	aag Lys	ctg Leu	gtg Val	tat Tyr 270	gga Gly	agc Ser	816
gg	cag	gac	ttt	ctc	tgg	cgc	ctg	gcc	cga	qcc	tac	agt	qac	ata	tat	864

	Arg	Gln	Asp 275	Phe	Leu	Trp	Arg	Leu 280	Ala	Arg	Ala	Tyr	Ser 285		Met	Cys	
						gtg Val	_		-	_			-		-		912
						gct Ala 310					_	-		-	-	-	960
						gcg Ala								-			1008
						atc Ile											1056
						ctc Leu			_			_	-				1104
						tat Tyr						-					1152
						ttg Leu 390											1200
						ttc Phe											1248
			Ala			gta Val											1296
		Asn				aga Arg	Trp										1344
(gat	gtc	acg	aag	gag	gat	ttg	gct	atc	cag	aag	gac	ctg	gaa	gaa	ctg	1392

Asp Val Thr Lys Glu Asp Leu Ala Ile Gln Lys Asp Leu Glu Glu Leu 455 gaa gtc att tta cga gac taa 1413 Glu Val Ile Leu Arg Asp 465 470 <210> 210 <211> 470 <212> PRT <213> Homo sapiens <400> 210 Met Ser Arg Leu Gly Ala Leu Gly Gly Ala Arg Ala Gly Leu Gly Leu Leu Leu Gly Thr Ala Ala Gly Leu Gly Phe Leu Cys Leu Leu Tyr Ser 25 Gln Arg Trp Lys Arg Thr Gln Arg His Gly Arg Ser Gln Ser Leu Pro Asn Ser Leu Asp Tyr Thr Gln Thr Ser Asp Pro Gly Arg His Val Met Leu Leu Arg Ala Val Pro Gly Gly Ala Gly Asp Ala Ser Val Leu Pro 70 75 Ser Leu Pro Arg Glu Gly Gln Glu Lys Val Leu Asp Arg Leu Asp Phe Val Leu Thr Ser Leu Val Ala Leu Arg Arg Glu Val Glu Glu Leu Arg 105 Ser Ser Leu Arg Gly Leu Ala Gly Glu Ile Val Gly Glu Val Arg Cys 115 120 125 His Met Glu Glu Asn Gln Arg Val Ala Arg Arg Arg Phe Pro Phe Val Arg Glu Arg Ser Asp Ser Thr Gly Ser Ser Ser Val Tyr Phe Thr 150 155 Ala Ser Ser Gly Ala Thr Phe Thr Asp Ala Glu Ser Glu Gly Gly Tyr 170 Thr Thr Ala Asn Ala Glu Ser Asp Asn Glu Arg Asp Ser Asp Lys Glu 185 Ser Glu Asp Gly Glu Asp Glu Val Ser Cys Glu Thr Val Lys Met Gly 195 200 205 Arg Lys Asp Ser Leu Asp Leu Glu Glu Glu Ala Ala Ser Gly Ala Ser 220

Ser Ala Leu Glu Ala Gly Gly Ser Ser Gly Leu Glu Asp Val Leu Pro

235

Leu	Leu	Gln	Gln	A1a 245		Glu	Leu	His	Arg 250		Asp	Glu	Gln	Gly 255	-	
Arg	Glu	Gly	Phe 260	G1n	Leu	Leu	Leu	Asn 265		Lys	Leu	۷a٦	Tyr 270	Gly		
Arg	Gln	Asp 275	Phe	Leu	Trp	Arg	Leu 280		Arg	Ala	Tyr	Ser 285	Asp		Cys	
Glu	Leu 290	Thr	Glu	Glu	Val	Ser 295	Glu	Lys	Lys	Ser	Tyr 300		Leu	Asp	Gly	
Lys 305	Glu	Glu	Ala	Glu	Ala 310	Ala	Leu	Glu	Lys	Gly 315		Glu	Ser	A1 a	Asp 320	
Cys	His	Leu	Trp	Tyr 325	Ala	Val	Leu	Cys	Gly 330	Gln	Leu	Ala	Glu	His 335	Glu	
Ser	Ile	Gln	Arg 340	Arg	Пe	G1n	Ser	G1y 345	Phe	Ser	Phe	Lys	G1u 350	His	Val	
	Lys	355					360					365				
	G1y 370					375					380					
385	Thr				390					395					400	
	Ala			405				0	410					415		
Ser	Lys	Ala	G1y 420	Arg	Val	Tyr	Ile	Ser 425	Lys	Cys	Tyr	Arg	G1u 430	Leu	Gly	
Lys	Asn	Ser 435	Glu	Ala	Arg	Trp	Trp 440	Met	Lys	Leu	Ala	Leu 445	Glu	Leu	Pro	
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						tat Tyr 55					_	_		-	-	192
						acg Thr										240
						aag Lys										288
						ctg Leu										336
						aag Lys			_	-			_	_		384
						atg Met 135										432
						gat Asp										480
						gag Glu										528
ggc Gly	aca Thr	cgg Arg	ttc Phe 180	acg Thr	gag G1u	aag Lys	aag Lys	cat His 185	gag Glu	atc Ile	agc Ser	atg Met	cag Gln 190	gtg Val	gcc Ala	576

		Gly										acc Thr	624
	Phe	gcc Ala											672
		tgt Cys											720
		cta Leu							-		-		768
		ctg Leu 260	-	-		_	-	-	 	•	_	_	816
		aag Lys											864
		ggc Gly						-				~ ~	912
		ctc Leu											960
		cag Gln				Met							1008
		agc Ser 340										-	1056
Trp		att Ile			Thr								1104

aac tot gac ago aag cag aaa otg aat gac tga 1137 Asn Ser Asp Ser Lys Gln Lys Leu Asn Asp * <210> 212 <211> 378 <212> PRT <213> Homo sapiens <400> 212 Met Asp Leu Ala Gly Leu Leu Lys Ser Gln Phe Leu Cys His Leu Val Phe Cys Tyr Val Phe Ile Ala Ser Gly Leu Ile Ile Asn Thr Ile Gln 25 Leu Phe Thr Leu Leu Leu Trp Pro Ile Asn Lys Gln Leu Phe Arg Lys Ile Asn Cys Arg Leu Ser Tyr Cys Ile Ser Ser Gln Leu Val Met Leu Leu Glu Trp Trp Ser Gly Thr Glu Cys Thr Ile Phe Thr Asp Pro Arg Ala Tyr Leu Lys Tyr Gly Lys Glu Asn Ala Ile Val Val Leu Asn His 85 90 Lys Phe Glu Ile Asp Phe Leu Cys Gly Trp Ser Leu Ser Glu Arg Phe Gly Leu Leu Gly Gly Ser Lys Val Leu Ala Lys Lys Glu Leu Ala Tyr 120 125 Val Pro Ile Ile Gly Trp Met Trp Tyr Phe Thr Glu Met Val Phe Cys 135 Ser Arg Lys Trp Glu Gln Asp Arg Lys Thr Val Ala Thr Ser Leu Gln 150 155 His Leu Arg Asp Tyr Pro Glu Lys Tyr Phe Phe Leu Ile His Cys Glu 165 170 Gly Thr Arg Phe Thr Glu Lys Lys His Glu Ile Ser Met Gln Val Ala 185 Arg Ala Lys Gly Leu Pro Arg Leu Lys His His Leu Leu Pro Arg Thr 200 Lys Gly Phe Ala Ile Thr Val Arg Ser Leu Arg Asn Val Val Ser Ala 215 220 Val Tyr Asp Cys Thr Leu Asn Phe Arg Asn Asn Glu Asn Pro Thr Leu 230 235 Leu Gly Val Leu Asn Gly Lys Lys Tyr His Ala Asp Leu Tyr Val Arg 245 250

Arg	Ile	Pro	Leu 260		Asp	Ile	Pro	Glu 265		Asp	Asp	Gl.	Cys 270		` Ala	
Trp	Leu	His 275		Leu	Tyr	Gln	G1u 280		Asp	Ala	Phe	Glr 285		Glu	Tyr	
Tyr	Arg 290		Gly	Thr	Phe	Pro 295		Thr	Pro	Met	Val 300	Pro		Arg	Arg	
Pro 305	Trp	Thr	Leu	Val	Asn 310		Leu	Phe	Trp	Ala 315		Leu	Val	Leu	Tyr 320	
Pro	Phe	Phe	Gln	Phe 325		Val	Ser	Met	Ile 330		Ser	Gly	Ser	Ser 335	Leu	
Thr	Leu	Ala	Ser 340	Phe	Ile	Leu	Val	Phe 345	Phe	Val	Ala	Ser	Val 350	Gly		
Arg	Trp	Met 355	Пe	Gly	Val	Thr	G1u 360	Ile	Asp	Lys	Gly	Ser 365		Tyr	Gly	
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	gtg Val															96
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							cac His 120						Pro			38	34
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											ttg Leu					384
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											gga Gly					528
		Пe									agc Ser					576
	Asp										tat Tyr					624
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 Gly
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 Ile
 Phe
 Arg
 Ser
 His
 Thr
 Glu

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 Lys
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Phe	Tyr	Ser 275	Val	Pro	Tyr	Phe	Va1 280	Thr	Ala	Leu	Tyr	Gly 285	Leu	Val	Val
Pro	Gly 290	Cys	Ser	Trp		Pro 295	Asp	Ile	Thr	Leu	Ile 300	His	Ala	Gly	Gly
Leu 305	Ala	Gln	Ala	Gln	Phe 310	Ser	His	He	Gly	Ala 315	Ser	Leu	His	Ala	Arg 320
Thr	Ala	Tyr	Val	Tyr 325	Arg	Val	Pro	Glu	G1u 330		Lys	Ile	Leu	Phe 335	
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									aag Lys							144
									ttg Leu							192
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Val Pro Asp Ile Cys Asp Lys Phe Lys Gln Ile Thr Lys Gly Ser Phe
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Trp Ala Ser Val Ser Ala Gln Thr Asp Ala Thr Pro Ala Val Thr Thr
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									tct Ser							336
									caa G1n							384
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cag Gln 145	att Ile	aat Asn	cca Pro	tct Ser	att Ile 150	ttc Phe	tgc Cys	att Ile	cat His	att Ile 155	aca Thr	aac Asn	tat Tyr	aaa Lys	cct Pro 160	480
gca Ala	tta Leu	tcc Ser	ttt Phe	att Ile 165	aat Asn	cca Pro	gaa Glu	gta Val	cct Pro 170	gat Asp	gaa Glu	aac Asn	aat Asn	ttt Phe 175	gat Asp	528
aca Thr	ttg Leu	Met	aaa Lys 180	aca Thr	tct Ser	gat Asp	Gly	ttt Phe 185	aca Thr	ttg Leu	aat Asn	gct Ala	gaa Glu 190	tca Ser	tat Tyr	576
jtt /al:	Ser	ttc Phe 195	aca Thr	acc Thr	aaa Lys	Leu	gat Asp 200	att Ile	cct Pro	act Thr	gct Ala	gct Ala 205	aaa Lys	tat Tyr	gag Glu	624

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tco Ser 225	ctg Leu	aca Thr	tca Ser	tct Ser	ctg Leu 230	Cys	act Thr	gat Asp	aat Asn	aac Asn 235	Pro	gca Ala	gcg Ala	ttt Phe	ctg Leu 240	720
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	gaa Glu															816
	agg Arg															864
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ggt Gly	gaa Glu	gtc Val	acc Thr 340	aaa Lys	gct Ala	gat Asp	ctc Leu	tca Ser 345	ttc Phe	gtt Val	ctg Leu	999 Gly	aca Thr 350	gtt Val	agc Ser	1056
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							gtt Val					1536
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		He					act Thr			Asp		1680

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	Leu	Ser	Pro	A1 a 85		Cys	Asp	Ile	Asn 90	Cys	Cys	Cys	Asp	Pro 95		
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		Asn	Pro	Ser			Cys	Пe	His			Asn	Tyr	Lys		
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Ala	Leu	261	Phe	165	ASII	FIU	uiu	Val	170	ASP	ulu	ASII	ASII	175	ASP	
Thr	Leu	Met	Lys 180		Ser	Asp	Gly	Phe 185		Leu	Asn	Ala	G1u 190		Tyr	
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465			Pro		470					475					480
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Arg	Lys	•	Ser 500							Leu				Val	Lys
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Ser	Ala	Pro	Ala	G1u 565	Ala	Gly	Phe	Arg	Ala 570	Pro	Pro	Ala	Пe	Asn 575	Ala

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Ala	Trp	Cys	Leu	Trp 245		Gln	Arg	Arg	Leu 250		His	Val	Arg	Lys 255	Cys	
Val	Val	۷al	Val 260		Leu	Leu	Gln	Gly 265		Ser	Leu	Leu	G1u 270		Leu	•
Asp	Phe	Pro 275		Leu	Phe	Trp	Va1 280		Asp	Ala	His	A1a 285		Trp	His	
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						gac Asp											336
						acc Thr											384
cgg Arg	gag Glu 130	atc Ile	gaa Glu	cac His	gtc Val	atg Met 135	tac Tyr	cat His	gac Asp	tgg Trp	cgg Arg 140	ctg Leu	gtg Val	ccc Pro	aag Lys		432
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Arg Leu Pro Val Arg Ala Trp Ala Asp Val Arg Arg Glu Xaa Arg Leu
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Leu Gln Leu Leu Gly Arg Leu Pro Leu Phe Gly Leu Gly Arg Leu Val
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Thr Arg Lys Ser Trp Leu Trp Gln His Asp Glu Pro Cys Tyr Trp Arg
Leu Thr Arg Val Arg Pro Asp Tyr Thr Ala Gln Asn Leu Asp His Gly
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Lys Ala Trp Gly Ile Leu Thr Phe Lys Gly Lys Thr Glu Ser Glu Ala
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His Glu Glu Glu Ala Phe Thr Ala Phe Thr Pro Ala Pro Glu Asp Ser
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Glu Arg Gln Lys Asn Gly Asp Thr Ser Thr Glu Glu Pro Met Leu Asn
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				ctg ggc atc Leu Gly Ile	
		Lys Leu Leu		ttg gtg tgt Leu Val Cys	
				tct gtg gaa Ser Val Glu 95	
Ile Pro Tyr			Thr Lys Ala	aag ttc cac Lys Phe His 110	
Thr Val Gly I	His Glu Thr	Val Met Gly	cgg ttg atg Arg Leu Met		cct 384 Pro
gct cca gat a Ala Pro Asp a 130	aac ttt gac Asn Phe Asp	cag gag cct Gln Glu Pro 135	ata ctg gac Ile Leu Asp 140	tct ttc aac Ser Phe Asn	ttc 432 Phe
tct caa gaa s Ser Gln Glu l	tac ctt ttc Tyr Leu Phe	cag gag cag Gln Glu Gln	tac ctg tcc Tyr Leu Ser	aag gat ttg Lys Asp Leu	aca 480 Thr

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		age egg eta gee tte ea Cys Arg Leu Ala Phe H 220	
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		tc ggc cag agc ggc aa he Gly Gln Ser Gly Ly 300	
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Lys Pro Val Thr Cys Pro Arg Leu Cys Leu Val Ile Gly Ser Arg Leu
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Asp Ala Asp Ile His Thr Asn Thr Cys Arg Leu Ala Phe His Gly Ile
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Leu Leu His Gly Leu Glu Asp Arg Asn Tyr Ala Asp Ser Phe Leu Pro
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Arg Leu Lys Val Tyr Lys Leu Lys His Lys His Gly Leu Val Glu Arg
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Thr Asn Ile Gln Leu Phe Val Gly Leu Lys Val His Leu Ser Thr Gly
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Ile His Ile Pro Gly Gly Leu Ser Pro Glu Ser Lys Lys Ile Leu Thr
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Pro Ala Leu Lys Lys Arg Ala Arg Ala Gly Arg Gly Glu Ala Thr Arg
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Gln Glu Glu Ser Ala Glu Arg Xaa Arg Pro Ser Gln His Val Val Leu
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acc Thr 65	Gly	ctc Leu	cca Pro	gcc Ala	cta Leu 70	gac Asp	cag G1n	ctc Leu	tta Leu	ggt Gly 75	gga Gly	ggt Gly	tta Leu	gcc Ala	gtt Val 80	240
gga Gly	aca Thr	gtt Val	ctt Leu	cta Leu 85	att Ile	gag Glu	gag Glu	gat Asp	aaa Lys 90	tat Tyr	aat Asn	att Ile	tac Tyr	tca Ser 95	cct Pro	288
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ctt Leu	cca Pro 130	gca Ala	Pro	tta Leu	Leu	Asp	Asp	aaa Lys	tgt Cys	aaa Lys	aag Lys 140	gaa Glu	ttt Phe	gat Asp	gaa Glu	432
gat Asp 145	gta Val	tac Tyr	aat Asn	cat His	aaa Lys 150	aca Thr	cca Pro	gaa Glu	tct Ser	aat Asn 155	att Ile	aag Lys	atg Met	aaa Lys	ata Ile 160	480
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	ttt Phe 180				-	_		_	_		576
	gag Glu	_									624
	act Thr										672
	ctt Leu										720
	aat Asn		-		-	_			-		 768
	ctt Leu 260										816
	 ggc Gly		-	_			_			_	864
	ctg Leu										912
	atc Ile										960
	gta Val										1008
	ttg Leu 340										1056

att Ile	cct Pro	cgg Arg 355	ctt Leu	aat Asn	aac Asn	ttg Leu	atc Ile 360	Cys	gat Asp	gaa Glu	tca Ser	gat Asp 365	gtc Val	aaa Lys	gac Asp	1104
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Gly	Pro	Arg 35		Ser	Val				Ser	Gly	Pro	Arg 45		Val	Ser	
Пе	Ala 50	Gly	Thr	Arg				Arg	Asn		G1n 60		Leu	Val	Ser	
Thr 65		Leu	Pro				Gln	Leu	Leu			Gly	Leu		Val 80	
	Thr	Val	Leu		-	Glu	Glu .	Asp	Lys		Asn	Ile	Tyr			

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Leu	Leu	Ph∈	Lys 100		Phe	Leu	ı Ala	GTu 105		∕ Il∈	val	Asn	ر G ا 110		Th
Leu	Leu	Val 115	Ala ;	Ser	Ala	Lys	Glu 120		Pro	Ala	Asr	11e 125	Leu		Glu
Leu	Pro 130		Pro	Leu	Leu	Asp 135		Lys	Cys	Lys	Lys 140		Phe	Asp	G1ı
Asp 145	Val	Tyr	Asn	His	Lys 150	Thr	Pro	Glu	Ser	Asn 155		Lys	Met	Lys	I16 160
Ala	Trp	Arg	Tyr	G1n 165		Leu	Pro	Lys	Met 170		Ile	Gly	Pro	Val 175	Ser
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			Leu 260					265					270		
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305			Ile		310					315					320
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			Leu 340					345					350	-	
		.355	Leu				360					365			·
	A1a 370	Phe	Lys	Leu	Lys	Arg 375	Lys	Leu	Phe	Thr	Ile 380	Glu	Arg	Leu	His
385			Asp		390					395					400
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tat Tyr	aca Thr	cgg Arg	ctg Leu 100	cca Pro	cat His	ctg Leu	ctg Leu	aaa Lys 105	acc Thr	aaa Lys	ctt Leu	gag Glu	gac Asp 110	gcc Ala	aat Asn	336
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atg 1et	gcg Ala	gac Asp	ctc Leu	cta Leu	cag Gln	cag Gln	ggt Gly	cct Pro	gat Asp	gtg Val	gca Ala	ccc Pro	agc Ser	ttc Phe	ctc Leu	432

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gtc Val	agc Ser	ctg Leu 195	Leu	cgt Arg	gtc Val	ttg Leu	gag Glu 200	Met	act Thr	atc Ile	aca Thr	ctg Leu 205	gtg Val	cct Pro	gag Glu	624
		Leu										ctg Leu				672
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												ggc Gly				768
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ctc Leu	ctg Leu	gtg Val 275	cgt Arg	ggc Gly	cca Pro	gcc Ala	tca Ser 280	gag Glu	aga Arg	gag Glu	caa G1n	gcc Ala 285	aca Thr	tca Ser	gtg Val	864
										Ser		tgc Cys				912
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Arg Lys Arg Phe S	tcc ctg cag agc Ser Leu Gln Ser 325	tat gcg gat tat a Tyr Ala Asp Tyr I 330	tc agt gcc gat 1008 le Ser Ala Asp 335
gag ctg gcc caa g Glu Leu Ala Gln V 340	jtg gaa cag atg /al Glu Gln Met	ctg gcg cac ctg a Leu Ala His Leu T 345	cc tct gca tct 1056 hr Ser Ala Ser 350
gcc cag gca gca g Ala Gln Ala Ala A 355	gct gcc tcc ctg Na Ala Ser Leu 360	ccc acc agt gag g Pro Thr Ser Glu G 3	ag gac tct gcc 1104 lu Asp Ser Ala 65
cca tct gct atg c Pro Ser Ala Met P 370	ecc acc cca tct Pro Thr Pro Ser 375	ctg ctg tgt tcc a Leu Leu Cys Ser S 380	gc cct gtg gcc 1152 er Pro Val Ala
aca agt cct gca a Thr Ser Pro Ala L 385			1188
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Met Glu Glu Leu Pi 1 ! Ile Leu Ala Lys H 20 Arg Asp Ser Leu Me	5 is Phe Ala Asp et Gln Ala Leu .	10 Ala Arg Ile Val Gl 25 Ala Ser Tyr Val Cy	15 y Thr Asp Ile 30 rs Tyr Pro His
Met Glu Glu Leu Pi 1 ! Ile Leu Ala Lys H 20 Arg Asp Ser Leu Me 35	5 is Phe Ala Asp et Gln Ala Leu 40	10 Ala Arg Ile Val Gl 25 Ala Ser Tyr Val Cy 45 Pro Glu Glu Gln Ar	15 y Thr Asp Ile 30 ys Tyr Pro His
Met Glu Glu Leu Pr 1 ! Ile Leu Ala Lys Hr 20 Arg Asp Ser Leu Me 35 Ser Leu Arg Ala Va 50	5 is Phe Ala Asp et Gln Ala Leu 40 al Glu Arg Ile 55	10 Ala Arg Ile Val Gl 25 Ala Ser Tyr Val Cy 45	15 y Thr Asp Ile 30 ys Tyr Pro His g Ile Ala Met p Ala Gln Thr
Met Glu Glu Leu Pr 1	5 is Phe Ala Asp et Gln Ala Leu 40 al Glu Arg Ile 55 eu Ala Pro Tyr (70 al Arg Leu Trp /	10 Ala Arg Ile Val Gl 25 Ala Ser Tyr Val Cy 45 Pro Glu Glu Gln Ar 60 Glu Gln Arg Pro Tr 75	15 y Thr Asp Ile 30 ys Tyr Pro His g Ile Ala Met p Ala Gln Thr 80
Met Glu Glu Leu Pr 1	5 is Phe Ala Asp et Gln Ala Leu 40 al Glu Arg Ile 55 eu Ala Pro Tyr (70 al Arg Leu Trp / 5 ro His Leu Leu I	10 Ala Arg Ile Val Gl 25 Ala Ser Tyr Val Cy 45 Pro Glu Glu Gln Ar 60 Glu Gln Arg Pro Tr 75 Arg Gly Cys Gly Ph 90 Lys Thr Lys Leu Gl	15 y Thr Asp Ile 30 ys Tyr Pro His g Ile Ala Met p Ala Gln Thr 80 e Gly Tyr Arg 95 u Asp Ala Asn 110

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Asn 145		Va1	Leu	Asn	G1n 150		Asn	Trp	Ala	Phe 155	Ser	Glu	Phe	Ile	Gly 160
Met	Ile	Gln	Glu	Ile 165	Gln		Ala	Ala	Glu 170		Leu	Glu	Arg	Asn 175	Phe
Va1	Asp	Ser	Arg 180	Gln		Lys	Val	Cys 185	Ala	Thr	Cys	Phe	Asp 190	Leu	Ser
Val	Ser	Leu 195	Leu		Val	Leu	G1u 200	Met		Пe	Thr	Leu 205	Val	Pro	Glu
Ile	Phe 210			Trp	Thr	Arg 215	Pro		Ser	Glu	Met 220			Arg	Arg
Leu 225	Ala	G1n	Leu	Leu	Asn 230			Leu	Asn	Arg 235	Val	Thr	Ala	Glu	Arg 240
		Phe	Asp	Arg 245		Val	Thr	Leu	Arg 250		Pro	Gly	Leu	G1u 255	
Val	Asp	His	Tyr 260		Ile	Leu	Val	A1a 265		Thr	Gly	Пe	Leu 270		Gln
Leu	Leu	Val 275	Arg	Gly	Pro	Ala	Ser 280		Arg	G1u	Gln	Ala 285		Ser	Val
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Arg	Lys	Arg	Phe	Ser 325	Leu	Gln	Ser	Tyr	A1a 330		Tyr	Пe	Ser	A1a 335	
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Ala	Gln	A1a 355	Ala	Ala	Ala	Ser	Leu 360	Pro	Thr	Ser	Glu	G1u 365	Asp	Ser	Ala
Pro	Ser 370	Ala	Met	Pro		Pro 375	Ser	Leu	Leu	Cys	Ser 380	Ser	Pro	Val	Ala
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aaa Lys	tat Tyr	aat Asn	cag Gln 100	atc Ile	caa G1n	cta Leu	ttt Phe	gca Ala 105	ccg Pro	gcg Ala	gaa Glu	tgg Trp	gta Val 110	gcc Ala	ttg Leu	336
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145					150					155					160	
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							gtc Val									720
							ttt Phe									768
ata Ile	atg Met	aca Thr	atg Met 260	ctt Leu	aac Asn	aag Lys	ggc Gly	tca Ser 265	ata Ile	cat His	tct Ser	cag Gln	tca Ser 270	tct Ser	tca Ser	816
							att Ile 280									864
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aag Lys	agg Arg	tcc Ser	caa G1n	gat Asp	gta Val	cta Leu	cat His	cgc Arg	tat Tyr	ata Ile	gag Glu	gat Asp	gaa Glu	aga Arg	tta Leu	1008

325 330 335 agt ggt aaa tgc cct ctt cca agg caa caa gta aca gaa att ata ttt 1056 Ser Gly Lys Cys Pro Leu Pro Arg Gln Gln Val Thr Glu Ile Ile Phe 340 345 350 gtt tta aaa gca gtc agt act ctt att gat tca ctt aag aaa act cag 1104 Val Leu Lys Ala Val Ser Thr Leu Ile Asp Ser Leu Lys Lys Thr Gln 355 360 cct gag aat gtt gat gga aat acc tgg gca caa gta att gcc tta tac 1152 Pro Glu Asn Val Asp Gly Asn Thr Trp Ala Gln Val Ile Ala Leu Tyr 370 375 380 cca act tta gta gaa tgc atc acc tgt tct tct tca gaa gtc tgt tct 1200 Pro Thr Leu Val Glu Cys Ile Thr Cys Ser Ser Ser Glu Val Cys Ser 385 390 395 gca ctt aaa gag gca cta gtt cct ttt aag gat ttc atg cag cca cca 1248 Ala Leu Lys Glu Ala Leu Val Pro Phe Lys Asp Phe Met Gln Pro Pro 405 410 415 gca tcc aga gtt caa aat gga gaa tct tga 1278 Ala Ser Arg Val Gln Asn Gly Glu Ser * 420 425 <210> 238 <211> 425 <212> PRT <213> Homo sapiens <220> <221> VARIANT <222> (1)...(425) <223> Xaa = Any Amino Acid <400> 238 Met Asp Asp Leu Gln Lys Leu Gly Val Ile Leu His Ser Ala Ile Ser 5 10 15 Val Pro Ile Ser Ser Asp Ala Ser Pro Phe Ile Leu Pro Ser Tyr Thr 25 Glu Ala Val Leu Thr Ser Leu Gln Glu Ala Val Leu Thr Ala Leu Asp 40 45

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Tyr 65	Pro	Ala	Ile	Phe	Asp 70	Gln	Leu	l Leu	A) a	Phe 75	· Val	Glu	Phe	Ser	Cys 80
Lys	Pro	Pro	Gln	Tyr 85	Gly	Gln	Хаа	Glu	Thr 90	Lys	His	Ile	Ala	Asn 95	Αla
			100		Gln			105					110		
Asn	Tyr	Val 115		Phe	Ala	Glu	Arg 120		Leu	G Tu	۷a٦	Val 125		Asp	Leu
	130				Cys	135					140		-		
145					Thr 150					155			-	_	160
				165	Thr				170					175	
			180		Leu			185					190		_
		195			Trp		200					205			
	210				He	215					220				
225					Ile 230					235		•			240
				245	Ala				250					255	
			260		Asn			265					270		
		275			He		280					285			-
	290				Leu	295					300		•		
305					Tyr 310					315					320
				325	Val				330			·		335	
Ser	Gly	L.ys	Cys 340	Pro	Leu	Pro	Arg	G1n 345	Gln	Val	Thr	Glu	Ile 350	Ile	Phe
Val	Leu	Lys 355	Ala	Val	Ser	Thr	Leu 360	Ile	Asp	Ser	Leu	Lys 365	Lys	Thr	Gln
Pro	G1u 370	Asn	Val	Asp	Gly	Asn 375	Thr	Trp	Ala	Gln	Va1 380	Ile	Ala	Leu	Tyr
Pro 385	Thr	Leu	Val		Cys 390	Ile	Thr	Cys	Ser	Ser 395	Ser	Glu	Val	Cys	Ser 400

Ala	Leu	l Lys	Glu	A1a 405		ı Val	Pro	Phe	Lys 410) Phe	e Met	G1r	Pro 415	Pro	
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cca Pro	cca Pro	cat His 35	act Thr	gta Val	aat Asn	aca Thr	ctc Leu 40	ttc Phe	ctg Leu	acc Thr	aat Asn	gac Asp 45	ctg Leu	act Thr	gag Glu	144
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tac Tyr	tct Ser	Pro	cat His 100	aca Thr	gcc Ala	tat Tyr	gat Asp	gct Ala 105	gcg Ala	ccc Pro	cag Gln	ggc Gly	gtc Val 110	aac Asn	aac Asn	336
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Trp	Leu	Ala 115	Lys	Gly	Leu	Gly	Ala 120	-	Thr	Ser	Arg	Pro 125		His	Pro	
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											atg Met					48
											gct Ala					52
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											cat His 220					677
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											cgc Arg					768
		Arg									gtg Val					816
	Ser					Leu					gct Ala					864
aca	ggt	gag	atg	tcc	cat	cat	gat	act	ttg	gat	gct	gct	tcc	саа	qqa	912

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Sei	rne	Ald	G1u 20	ser.	rrp	ASP	ASII	25	ыу	Leu	Leu	vai	30	Pro	ser	
Pro	Pro	His 35	Thr	Val	Asn	Thr	Leu 40	Phe	Leu	Thr	Asn	Asp 45	Leu	Thr	Glu	
Glu	Va1 50		Glu	G1u	Val.	Leu 55		Lys	Lys	Ala	Asp 60		Пe	Leu	Ser	
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65 Trp	Lys	Glu	Arg	Leu	70 Val	Ile	Ara	Ala	Leu	75 G1u	Asn	Ara	Val	Glv	08 11e	
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Trp	Leu	Ala 115	Lys	Gly	Leu				Thr	Ser	Arg	Pro 125		His	Pro	
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Gln	Val	Val 195		Phe	Leu	Ser	Arg 200		Lys	Gln	Leu	Tyr 205		Lys	Thr	
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Arg	Пe	Lys	Arg	His 245	Leu	Lys	Leu	Ser	His 250	Ile	Arg	Leu	Ala	Leu 255	Gly	
Val	Gly	Arg	Thr 260	Leu	Glu	Ser	Gln	Va1 265	Lys	Val	Val	Ala	Leu 270			
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Ser	Asp	Leu	Arg	Asp 325	Met	Leu	Asp	Ser	His 330	Leu	Glu	Asn	Lys	Ile 335	Asn	
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caa Gln	gtt Val	gta Val 35	gtt Val	gag Glu:	tcc Ser	ctg Leu	tac Tyr 40	att Ile	atc Ile	agt Ser	tgc Cys	tat Tyr 45	ggc Gly	acc Thr	tta Leu	144

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			aca Thr					Pro			240
			aga Arg								288
		His	cct Pro 100								336
			gct Ala								384
			tct Ser								432
			tgg Trp								480
			ctg Leu								528
			caa Gln 180								576
	His		ccg Pro		Thr						624
Asp			gat Asp	Asn							672

	Val					Ser					Ser				gga Gly 240	720
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cac His	atg Met	tcc Ser 275	Ser	atg Met	gag Glu	cac His	acg Thr 280	gag Glu	gag Glu	ggc Gly	tcc Ser	999 Gly 285	Ser	gac Asp	ttg Leu	864
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Gln	Val	Va1 35		Glu	Ser	Leu	Tyr 40	25 Ile	IJе	Ser	Cys	Tyr 45	30 Gly	Thr	Leu	
/al	G1u 50		Met	Met	Glu	Pro 55	Arg	Pro	Leu	Ser	Thr 60		Pro	Lys	Ile	
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Ala Asn His Pro Leu Leu Leu Ala Ala Asp Ala Val Gln Tyr Tyr Gln
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Phe Leu Leu Ala Gly Leu Val Pro Pro Gly Ser Pro Gly Pro Ile Thr
                            120
Arg His Gly Ser Tyr Asp Ser Leu Ala Ser Asp His Ser Gly Gln Glu
                        135
                                            140
Asp Glu Glu Trp Leu Ser Gln Val Glu Ile Val Thr His Thr Gly Pro
                    150
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His Arg Arg Leu Trp Met Gly Pro Gln Phe Gln Phe Lys Thr Ile His
                165
                                    170
Pro Ser Gly Gln Thr Thr Val Ile Ser Ser Ser Ser Val Leu Gln
            180
                                185
Ser His Gly Pro Ser Asp Thr Pro Gln Pro Leu Leu Asp Phe Asp Thr
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Asp Asp Leu Asp Leu Asn Ser Leu Arg Ile Gln Pro Val Arg Ser Asp
                        215
                                            220
Pro Val Ser Met Pro Gly Ser Ser Arg Pro Val Ser Asp Arg Gly
                    230
                                        235
Val Ser Thr Val Ile Asp Ala Ala Ser Gly Thr Phe Asp Arg Ser Val
                245
                                    250
Thr Leu Leu Glu Val Cys Gly Ser Trp Pro Glu Gly Phe Gly Leu Arg
            260
                                265
His Met Ser Ser Met Glu His Thr Glu Glu Gly Ser Gly Ser Asp Leu
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Pro Thr Pro Trp Pro Ser His Leu Ala Gly Thr Ser Trp Asp Pro Glu
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Gln Thr Gln Pro Leu Thr
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											cct Pro					144
cgg Arg	ccc Pro 50	aac Asn	aca Thr	tcc Ser	cca Pro	gac Asp 55	cga Arg	ggt Gly	tct Ser	cgg Arg	gac Asp 60	cgg Arg	aag Lys	tca Ser	ggt Gly	192
ggg Gly 65	aga Arg	ctg Leu	ggc Gly	tcc Ser	ccg Pro 70	aag Lys	cca Pro	gag Glu	cgg Arg	cag Gln 75	aga Arg	ggc Gly	cag Gln	aac Asn	tcc Ser 80	240
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tcc Ser	aag Lys	agc Ser	tcc Ser 100	agc Ser	aag Lys	gtc Val	acg Thr	agc Ser 105	gtg Val	ccc Pro	ggc Gly	aaa Lys	gcc Ala 110	tcg Ser	gat Asp	336
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Arg Pro Asn Thr Ser Pro Asp Arg Gly Ser Arg Asp Arg Lys Ser Gly
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Gly Arg Leu Gly Ser Pro Lys Pro Glu Arg Gln Arg Gly Gln Asn Ser
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Lys Ala Pro Ala Ala Pro Ala Asp Arg Lys Arg Xaa Xaa Ser Pro Gln
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Ser Lys Ser Ser Ser Lys Val Thr Ser Val Pro Gly Lys Ala Ser Asp
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Pro Gly Ala Ala Ser Thr Lys Ser Gly Lys Ala Ser Thr Leu Ser Arg
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ctc ctc gca ggg ctt gca cta ctg gga gtc ggg ccg gtc cca gcg cgg
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Leu Leu Ala Gly Leu Ala Leu Leu Gly Val Gly Pro Val Pro Ala Arg
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acc Thr	ctt Leu 50	Ala	gct Ala	ttc Phe	ggg Gly	gac Asp 55	ctc Leu	aac Asn	tcc Ser	gac Asp	aag Lys 60	Gln	acg Thr	gat Asp	ctc Leu	192
						Asn					Phe				cag Gln 80	240
												ttc Phe			His	288
												gat Asp				336
												tat Tyr 125				384
gaa Glu	tta Leu 130	gga Gly	gct Ala	gtt Val	atc Ile	ttc Phe 135	tgg Trp	gga Gly	caa G1n	aat Asn	caa Gln 140	aca Thr	tta Leu	gat Asp	cct Pro	432
												gag Glu				480
			Asn									ggt Gly				528
gaa Glu :	tcc Ser	aac Asn	cag Gln 180	cca Pro	cag G1n	ata Ile	Leu	tta Leu 185	gga Gly	ggg Gly	aat Asn	tta Leu	tca Ser 190	tgg Trp	cat His	576
cca (Pro A	gca 41a	ttg Leu	acc Thr	act Thr	aca Thr	agt Ser	aaa Lys	atg Met	cga Arg	att Ile	cca Pro	cat His	tct Ser	cat His	gca Ala	624

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ttg Leu 225	ı Asn	gco Ala	acc Thr	act Thr	agt Ser 230	· Thr	tto Phe	cag Gln	ttt Phe	gaa Glu 235	ı Ile	tgg Trp	gaa Glu	aat Asn	ttg Leu 240	720
gat Asp	gga Gly	aac Asn	ttc Phe	tct Ser 245	Val	agt Ser	act Thr	ata Ile	ttg Leu 250	Glu	aaa Lys	cct Pro	caa G1n	aat Asn 255	atg Met	768
atg Met	gtg Val	gtt Val	gga Gly 260	G1n	tca Ser	gca Ala	ttt Phe	gca Ala 265	Asp	ttt Phe	gat Asp	gga Gly	gat Asp 270	gga Gly	cac His	816
atg Met	gat Asp	cat His 275	Leu	ctg Leu	cca Pro	ggc Gly	tgt Cys 280	gaa Glu	gat Asp	aaa Lys	aat Asn	tgc Cys 285	caa Gln	aag Lys	agt Ser	864
						tct Ser 295										912
caa G1n 305	gat Asp	ttc Phe	agc Ser	aat Asn	aag Lys 310	ggc Gly	aca Thr	ctc Leu	tgg Trp	ggc Gly 315	ttt Phe	gtg Val	cca Pro	ttt Phe	gtg Val 320	960
gat Asp	gaa Glu	cag Gln	caa Gln	cca Pro 325	act Thr	gaa Glu	ata Ile	cca Pro	att Ile 330	cca Pro	att Ile	acc Thr	ctt Leu	cat His 335	att Ile	1008
gga Gly	gac Asp	tac Tyr	aat Asn 340	atg Met	gat Asp	ggc Gly	tat Tyr	cca Pro 345	gac Asp	gct Ala	ctg Leu	gtc Val	ata Ile 350	cta Leu	aag Lys	1056
aac Asn	Thr	tct Ser 355	gga Gly	agc Ser	aac Asn	cag Gln	cag Gln 360	gcc Ala	ttt Phe	tta Leu	ctg Leu	gag G1u 365	aac Asn	gtc Val	cct Pro	1104
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			aca Thr 420											Asn		129	96
			gat Asp													134	14
			gac Asp									Gly				139	2
cct Pro 465	gga Gly	cct Pro	tat Tyr	atc Ile	atg Met 470	tat Tyr	aca Thr	act Thr	gta Val	gat Asp 4 75	gca Ala	aat Asn	999 Gly	tat Tyr	ctg Leu 480	144	.0
			tca Ser													148	8
caa Gln	cta Leu	cca Pro	tac Tyr 500	aac Asn	gtg Val	ctt Leu	ggt Gly	tta Leu 505	ggt Gly	cgg Arg	agc Ser	gca Ala	aat Asn 510	ttt Phe	ctt Leu	153	6
gac Asp	cat His	ctc Leu 515	tac Tyr	gtt Val	ggt Gly	att Ile	ccc Pro 520	cgt Arg	cca Pro	tct Ser	gga Gly	gaa Glu 525	aaa Lys	tct Ser	ata Ile	158	4
Arg	aaa Lys 530	caa Gln	gag G1u	tgg Trp	Thr	gca Ala 535	atc Ile	att Ile	cca Pro	aat Asn	tcc Ser 540	cag Gln	cta Leu	att Ile	gtc Val	163	2
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545	,				550					555					560		
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									ggc Gly							1	776
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Glu	Ser		Gln 180	Pro		ı Ile	. Lei	Leu 185	G1y		Asn	Leu	Ser 190	Trp	His
Pro	Ala		Thr		Thr	Ser	Lys 200	Met		Ile	Pro	His 205	Ser		Ala
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Leu 225		Ala	Thr	Thr	Ser 230		Phe	Gln	Phe	G1u 235		Trp	Glu	Asn	Leu 240
				245					250		-			255	
			260					265					270		His
Met	Asp	His 275	Leu	Leu	Pro	Gly	Cys 280		Asp	Lys	Asn	Cys 285	Gln	Lys	Ser
Thr	Ile 290	Tyr	Leu	Val	Arg	Ser 295	Gly	Met	Lys	Gln	Trp 300	Val	Pro	Val	Leu
305					310		Thr		·	315					320
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	450					455	Lys				460	_			
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				485			Leu		490					495	
Gln	Leu	Pro	Tvr	Asn	Val	Leu	Glv	leu	Glv	Ara	Ser	Αla	Asn	Phe	Leu

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Ile 545	Pro	Tyr	Pro	His	Asn 550		Pro	Arg	Ser	Trp 555		Ala	Lys	Leu	Tyr 560	
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	ctt Leu 50										-					192
	aga Arg															240

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					Val					Ser					tcc Ser	288
														Gly	ttt Phe	336
			Phe					Asp					Leu	tat Tyr	gaa Glu	384
														agg Arg		432
					cca Pro 150			gcc Ala	taa *							462
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Thr	Leu	Cys 35	Gly	Gly	Leu	Tyr	Phe 40	Phe	Glu	Phe	Val	Ser 45	Cys	Ser	Ala	
Phe	Leu 50	Leu	Ser	Leu	Leu	I1e 55	Leu	Ile	Val	Tyr	Cys 60	Thr	Pro	Phe	Tyr	
Glu 65	Arg	Val	Asp	Thr	Thr 70	Lys	Val	Lys	Ser	Ser 75	Asp	Phe	Tyr	Ile	Thr 80	
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Ile	Ala	Ser		Met	Phe	Leu	Leu		Phe	Пe	Thr	Met		Tyr	Glu	

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		Asp							Ser		aac Asn	384
						cag Gln		Ser				432
						gcc Ala						480
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						tgc Cys						576
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						aac Asn						672
						cac His						720
		Asp				ggc G1y 250						768
	Asn				Val	ctc Leu		His				816

			ggc Gly													864
			atc Ile										_		-	912
	Pro		ctc Leu											_		960
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Phe	His	Met 35	Pro	Ile	Thr		Ala 40		Gln	Gly	Asp	Arg 45		Gly	Ile	
Cys	Va1 50		G1n	Phe				Leu	Leu		Arg 60	-	Leu	Val	Cys	

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Lys	Ile	Pro	Tyr	Phe 85	Arg	Gly	Pro	Leu	G1n 90	Thr	Lys	Ala	Lys	Phe 95	
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			Val 180					185					190		
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Val	Gln	Ser 355	Pro												
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WO 01/29221

372

PCT/US00/29052

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Lys	Asn	-A1a 35	Ser	Leu	Ile	Ser	Ala 40	Leu	Ser	Thr	Gly	Arg 45		Ser	His	
Ile	G1n 50	Thr	Pro	Val	Val	Ser 55	Ser	Thr	Pro	Arg	Leu 60		Thr	Ser	Glu	
Arg 65	Asn	Leu	Thr	Cys	G1y 70	His	Thr	Ser	۷al	I1e 75	Leu	Asn	Arg	Met	A1a 80	
Pro	Val	Leu	Pro	Ser 85	Val	Leu	Lys	Leu	Pro 90	Val	Arg	Ser	Leu	Thr 95		
Phe	Ser	Ala	Arg 100	Lys	Gly	Lys	Arg	Lys 105	Thr	۷a٦	Lys	Ala	Val 110	Ile	Asp	
Arg	Phe	Leu 115	Arg	Leu	His	Cys	Gly 120	Leu	Trp	Val ·	Arg	Arg 125	Lys	Ala	Gly	
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ctg Leu	ctc Leu	tcg Ser	ttc Phe 20	Leu	ttc Phe	atc Ile	aac Asn	aag Lys 25	Пe	ttc Phe	cgg Arg	cgc Arg	aag Lys 30	Thr	ttt Phe	96
gag Glu	gag Glu	gtg Val 35	Val	gcc Ala	gag Glu	aag Lys	cgt Arg 40	gcc Ala	ctg Leu	agc Ser	gcc Ala	aat Asn 45	ctc Leu	tac Tyr	aag Lys	144
gcg Ala	gcc Ala 50	ggt Gly	ggt Gly	gcc Ala	gct Ala	acc Thr 55	aag Lys	aag Lys	ccc Pro	aag Lys	aag Lys 60	aag Lys	gaa Glu	ctt Leu	aag Lys	192
cgc Arg 65	gaa Glu	aag Lys	aag Lys	caa Gln	cgt Arg 70	cag Gln	cgg Arg	gaa Glu	cag Gln	cag Gln 75	agg Arg	gat Asp	gtg Val	aac Asn	aac Asn 80	240
gag Glu	ccg Pro	gaa Glu	cca Pro	gag Glu 85	gaa Glu	gcc Ala	gaa Glu	gac Asp	tac Tyr 90	tcc Ser	gat Asp	ggt Gly	cag Gln	tcg Ser 95	gag Glu	288
												tcc Ser				336
gtt Val	gaa Glu	ttt Phe 115	gaa Glu	ccc Pro	gat Asp	gca Ala	gag Glu 120	gtc Val	ctc Leu	act Thr	gat Asp	cag Gln 125	cga Arg	cga Arg	ccc Pro	384
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gga	aag	aag	gat	aaa	cgt	taa										453

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Leu Leu Ser Phe Leu Phe Ile Asn Lys Ile Phe Arg Arg Lys Thr Phe
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Glu Glu Val Val Ala Glu Lys Arg Ala Leu Ser Ala Asn Leu Tyr Lys
Ala Ala Gly Gly Ala Ala Thr Lys Lys Pro Lys Lys Lys Glu Leu Lys
                        55
Arg Glu Lys Lys Gln Arg Gln Arg Glu Gln Gln Arg Asp Val Asn Asn
Glu Pro Glu Pro Glu Glu Ala Glu Asp Tyr Ser Asp Gly Gln Ser Glu
Gly Gln Gly Ser Val Ala Gly Glu Glu Pro Gly Leu Ser Lys Gln His
                                105
Val Glu Phe Glu Pro Asp Ala Glu Val Leu Thr Asp Gln Arg Arg Pro
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Ser Ser Val Ala Glu Lys Glu Asn Gln Pro Ser Gly Ala Gly Lys Lys
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Gly Lys Lys Asp Lys Arg
145
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			aag Lys 20													96
			agc Ser													144
			att Ile													192
tac Tyr 65	ctg Leu	gaa Glu	gga Gly	cca Pro	cct Pro 70	gga Gly	ttc Phe	att Ile	cat His	gga Gly 75	ggt Gly	gcc Ala	att Ile	gca Ala	acc Thr 80	240
			gct Ala													288
			gcc Ala 100													336
			gtt Val												agg Arg	384
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Met Ala Phe Leu Ser Pro Leu Val Leu Ile Cys His Pro Thr His Phe Leu Asp Pro Lys Leu Met Lys Glu Glu Gln Met Ser Gln Ala Gln Leu 20 25 Phe Thr Arg Ser Phe Asp Asp Gly Leu Gly Phe Glu Tyr Val Met Phe 45 Tyr Asn Asp Ile Glu Lys Arg Met Val Cys Leu Phe Gln Gly Gly Pro Tyr Leu Glu Gly Pro Pro Gly Phe Ile His Gly Gly Ala Ile Ala Thr 75 Met Ile Asp Ala Thr Val Gly Met Cys Ala Met Met Ala Gly Gly Ile 90 Val Met Thr Ala Asn Leu Asn Ile Asn Tyr Lys Arg Pro Ile Pro Leu 100 105 110 Cys Ser Val Val Met Ile Asn Ser Gln Leu Asp Lys Val Glu Gly Arg 120 Lys Phe Phe Val Ser Cys Asn Val Gln Ser Val Asp Glu Lys Thr Leu 135 Tyr Ser Glu Ala Thr Ser Leu Phe Ile Lys Leu Asn Pro Ala Lys Ser 145 150 155 Leu Thr

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ggt acc agt gct gga gtc cat gtc tac aac gta aaa cag cta aag ctt 96 Gly Thr Ser Ala Gly Val His Val Tyr Asn Val Lys Gln Leu Lys Leu 20 · 25 30

	-									_	_	gct Ala		144
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		-		_		-			-		_	cgg Arg		240
											-	act Thr 95		288
												ctt Leu		336
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His	Cys	Thr 35	Val	Pro	Ala	Tyr	Asn 40	Phe	Pro	Va1	Thr	Ala 45	Met	Ala	Ile	
Ala	Pro 50	Asn	Thr	Asn	Asn	Leu 55	Val	Ile	Ala	His	Ser 60	Asp	Gln	Gln	Val	
Phe 65	Glu	Tyr	Ser	Пe	Pro 70	Asp	Lys	Gln	Tyr	Thr 75	Asp	Trp	Ser	Arg	Thr 80	
	Gln	Lys	Gln	Gly 85	Phe	His	His	Leu	Trp 90		Gln	Arg	Asp	Thr 95		
Пe	Thr	His	Ile 100	Ser	Phe	His	Pro	Lys 105		Pro	Met	His	Ile 110	Leu	Leu	
His	Asp	Ala 115		Met	Phe	Cys	Ile 120		Asp	Lys	Ser	Leu 125	Pro	Leu	Pro	
Asn	Asp 130	Lys	Thr	Leu	Leu	Tyr 135	Asn	Pro	Phe	Pro	Pro 140	Thr	Asn	Asp	He	
Ile 145	Ala	Gln	Leu	Pro	Pro 150	Pro	Ile	Lys	Lys	Ly s 155	Lys	Phe	Gly	Thr		
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											cga Arg					96
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cag	cat	ctg	aga	gaa	agg	gat	tcc	aaa	cta	tac	ctc	cat	gag	ctc	cta	240

G1n 65	His	Leu	Arg	G1u	Arg 70	Asp	Ser	Lys	Leu	Tyr 75	Leu	His	Glu	Leu	Leu 80	
-		-	_								-			cgg Arg 95		288
														gcc Ala		336
														aca Thr		384
														ttg Leu		432
-											-		-	gct Ala	_	480
	-	-					-						-	atg Met 175	_	528
														ctg Leu	-	576
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Glu	Leu	Glu 35	Ala	Ala	Leu	Gly	Lys 40	Lys	His	Lys	Gly	Gly 45		Ser	Ser	
Ser	Gly 50	Pro	G1n	Arg	Leu	Va1 55	Ser	Phe	Arg	Leu	Ile 60	Arg	Asp	Leu	His	
G1n 65	His	Leu	Arg	Glu	Arg 70	Asp	Ser	Lys	Leu	Tyr 75	Leu	His	Glu	Leu	Leu 80	
Glu	Gly	Ser	Glu	I1e 85	Tyr	Leu	Pro	Glu	Va1 90	Val	Lys	Pro	Pro	Arg 95	Asn	
Pro	Glu	Leu	Val 100	Ala	Arg	Leu	Glu	Lys 105	Пe	Lys	Пe	Gln	Leu 110		Asn	
Glu	G1u	Tyr 115	Lys	Arg	Ile	Thr	Arg 120	Asn	Val	Thr	Cys	G1n 125	Asp	Thr	Arg	
His	Gly 130	Gly	Thr	Leu	Ser	Asp 135	Leu	Gly	Lys	Gln	Val 140	Arg	Ser	Leu	Lys	
Ala 145	Leu	Val	Ile	Thr	11e 150	Phe	Asn	Phe	Ile	Va1 155	Thr	Val	Val	Ala	Ala 160	
			Thr	165					170					175		
			Leu 180					185					190			
Glu	Leu	Tyr 195	Val	Met	Va1	Arg	A1a 200	Met	G1u	Gly	Glu	Leu 205	Gly	Glu	Leu	
		10>														
			1092													
		12>														
			Homo	sap	1 ens											
		20>	CDC													
		21> 22>	(1).	(1	092)											
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atg Met . 1	gcc Ala	gca Ala	gcg (Ala /	gcg Alal 5	atg Met	gcg Ala	gca Ala	gcg Ala	gca Ala 10	ggt Gly	gga Gly	999 Gly	gct Ala	ggc Gly 15	gcg Ala	48
gcc (cgc ·	tcc	ctc -	tcg (cgc	ttc	cga	ggc	tgc	ctg	gct	ggc	gcg	ctg	ctc	96

Ala	Arg	Ser	Leu 20		Arg	Phe	Arg	Gly 25	Cys	Leu	Ala	Gly	Ala 30		Leu	
			Val												ctg Leu	144
						gtc Val 55										192
						gaa Glu										240
						cag G1n										288
						aga Arg										336
						gga Gly										384
						gtc Val 135										432
						aat Asn										480
						gtc Val										528
						gcc Ala	Ser									576
ctg	cag	gcc	ctg	gct	gtg	cac	ctg	gcc	ttg	cag	ggc	gag	tct	tcc	agc	624

Leu	Gln	Ala 195	Ala	Val	His	Leu 200	Leu	Gln	Gly	G1u 205	Ser	Ser	Ser	
		Phe		caa G1n									ggt Gly	672
				ttg Leu 230										720
				ctg Leu										768
				gaa Glu										816
				ccc Pro										864
				atc Ile										912
				tca Ser 310										960
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	Gln			cgt Arg	Val				tga *	•				1092

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Leu 305		Tyr	Ser	· Ile	Ser 310		Gly	Gly	/ Asp	Thr 315		Thr	· Ile	Ala	Thr 320	
Met	Ala	Gly	Ala	11e 325	Ala		Ala	Tyr	Tyr 330	Gly		Asp	Glr	Val 335	Pro	
Glu	Ser	Trp	Gln 340		Ser	Cys	Glu	Gly 345		Glu	Glu	Thr	Asp 350	lle	Leu	
Ala	Gln	Ser 355		His	Arg	Val	Phe 360		Lys	Ser	•					
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			263													
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														ctc Leu		96
														cag Gln		144
														ctg Leu		192
														ctg Leu		240
														ctg Leu 95		288
ga	aga	qaq	cta	cad	caa	atc	сса	acc	cta	cta	cta	ccc	ata	cct	aca	336

Arg	Gly	Glu	Leu 100	Gln	Arg	Val	Pro	Thr 105	Leu	Leu	Leu	Pro	Met 110	Pro	Thr	
-	-	_	Leu			-				-	cca Pro	-		_		384
											tct Ser 140					432
											cta Leu					480
											gct Ala					528
											ctg Leu					576
											cag G1n					624
										-	ctc Leu 220			_	_	672
											cat His					720
tct Ser	ttt Phe	999 Gly	gac Asp	cac His 245	ctc Leu	ttt Phe	ggg Gly	Ala	ctg Leu 250	gtc Val	ctc Leu	ctg Leu	ccc Pro	ctg Leu 255	cag G1n	768
		Phe					Arg				ttt Phe	Gly				816
gga .	acc	tta	cda	act	cta	age	cta	cct	cta	acc	caa	tto	rct	ata	tcc	864

Gly	Ala	Leu 275	Arg	Ala	Leu	Ser	Leu 280	Pro	Leu	Thr	Gln	Leu 285	Pro	Val	Ser	
-	gag Glu 290	_						_	_		_	~			_	912
	tac Tyr															960
	gtg Val			-		-		_		-		-				1008
	cag G1n	-		_	-		-		-		_	-	-		_	1056
_	ctg Leu	_				_	_	_	_				~ ~			1104
	ctg Leu 370			_					-						-	1152
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Glu	Arg	Thr 35	Ser	Gly	Gly	Pro	G1u 40	Ala	Ala	Asp	Phe	Ser 45	Asp	Gln	Leu
Ser	Leu 50	Gly	Ser	Ser	Arg	Val 55	Pro	Arg	Cys	Gly	G1n 60	Gly	Thr	Leu	Leu
Ala 65	Gln	Ala	Cys	Gln	Asp 70	Leu	Pro	Ser	Ile	Arg 75	Asn	Cys	Tyr	Leu	Thr 80
His	Cys	Ser	Pro	A1a 85	Arg	Ala	Ser	Leu	Leu 90	Ala	Ser	Gln	Ala	Leu 95	His
Arg	Gly	Glu	Leu 100	Gln	Arg	Val	Pro	Thr 105	Leu	Leu	Leu	Pro	Met 110	Pro	Thr
		115					120	Pro				125		_	
	130					135		Ser			140			-	
145					150			Gln	•	155					160
				165				Val	170				_	175	
_			180					Asp 185					190		
		195					200	Leu				205			
	210					215		Asp			220				
225			•		230			Phe		235					240
			,	245				Ala	250					255	
			260					Leu 265				-	270		
		275					280	Pro				285			
Leu	G1u 290	Cys	Tyr	Thr	Val	Pro 295	Pro	Glu	Asp	Asn	Leu 300	Ala	Leu	Leu	Gln
Leu 305	Tyr	Phe	Arg		Leu 310	Val	Thr	Gly	Ala	Leu 315	Arg	Pro	Arg	Trp	Cys 320
Pro	Val	Leu	Tyr	Ala 325	Val	Ala	Val	Ala	His 330	Val	Asn	Ser	Phe	Ile 335	Phe
			340					G1u 345					350		
Met	Leu	G1n 355	Lys	Thr	Trp		Leu 360	Ala	Asp	G1u	Gly	Leu 365	Arg	Gln	His

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	Ser	Thr	Val	Leu 405	Gln	Asn	Gly	Val	Ser 410			100	
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					gcc Ala								96
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					ttc Phe								192
					gga G1y 70								240
					ctg Leu								288
					agg Arg								336

		atc Ile 115									-		_		-	384
		aga Arg														432
	Met	gag Glu														480
		cag Gln								_	_			-	-	528
		ata Ile													tga *	576
	<; <;	210> 211> 212> 213>	191 PRT	sap	oiens	5										
Mot		400>		۸٦,-	C1	\ an	۸٦ -	٨٠٠٠	47.5	Lau	Db a	A.a.=	۵۵.	01	V-3	
1		Gly		5					10					15		
Cys	Ala	Ala	Leu 20	Glu	Ala	Trp	Pro	Ala 25	Leu	Gln	Пe	Ala	Val 30	Glu	Asn	
Gly	Phe	Gly 35		Val	His	Ser	G]n 40		Lys	Ala	Lys	Trp 45		Gly	Gly	
Ala	Val 50	Glu	Asp	Tyr	Phe	Met 55		Asn	Ala	Asp	Leu 60		Leu	Asp	Glu	
Val 65		Asp	Phe	Leu	Gly 70		Leu	Leu	Thr	Asn 75		Phe	Asp	Thr	Val 80	
	Glu	Asp	Gly	Ser 85		Pro	G1n	Val			Gln	Leu	Gln			
Phe	His	His	Phe 100		Arg	Gly	Asp	Gly 105	90 Ala	Ala	Leu	Arg	Glu 110	95 Met	Ala	
Ser							_									

Thr	Ala 130	Arg	Glu	Thr	Asp	G1u 135		Glu	Asp	Asp	Val 140		Ser	Val	Glu		
G1u 145		Glu	Val	Thr	Ala 150		Asn	Asp	Gly	Ala 155	Ala		Asp	Gly	Val 160		
Cys	Pro	Gln	Pro	Glu 165		Ser	Asp	Pro	Asp 170		Gln	Thr	Ile	Lys 175			
Glu	Asp	Пe	Val 180		Asp	Gly	Trp	Thr 185		Val	Arg	Arg	Lys 190	-			
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			ggc Gly													8	48
			gcg Ala 20													,	96
			agt Ser													1	44
			ttt Phe													1!	92
ett eu 65	gtc Val	ccc Pro	gct Ala	gaa Glu	cct Pro 70	cca Pro	gag Glu	gcc Ala	tgc Cys	999 Gly 75	gaa Glu	ctc Leu	agc Ser	aac Asn	ggt Gly 80	24	40
tc he	ttc Phe	atc Ile	cag Gln	gac Asp 85	cag Gln	att Ile	gct Ala	ctg Leu	gtg Val 90	gag Glu	agg Arg	999 Gly	ggc Gly	tgc Cys 95	tcc Ser	28	38
tc	ctc	tcc	aaa	act	caa	ata	atc	саа	аао	cac	aac	aaa	caa	aca	ata	3′	36

Phe	Leu	Ser	Lys 100	Thr	Arg	Val	Val	Gln 105		His	Gly	Gly	Arg 110	Ala	Val	
			gac Asp												_	384
			agt Ser													432
			gac Asp													480
			gcc Ala										-			528
			ctg Leu 180									tag *				567
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Ala	Cys	Val	A1a 20	Ala	His	Gly	Phe	Arg 25	Ile	His	Asp	Tyr	Leu 30	Tyr	Phe	
Gln	Val	Leu 35	Ser	Pro	Gly	Asp	Ile 40		Tyr	Пе	Phe	Thr 45		Thr	Pro	
Ala	Lys 50		Phe	Gly	Gly	Ile 55		His	Thr	Arg	Tyr 60		Gln	Ile	His	
Leu 65		Pro	Ala	Glu	Pro 70		Glu	Ala	Cys	Gly 75		Leu	Ser	Asn	Gly 80	
	Phe	Пe	Gln	Asp 85		Пе	Ala	Leu	Va1 90		Arg	Gly	Gly	Cys 95		
Phe	Leu	Ser	Lys 100		Arg	Val	Val	Gln 105		His	Gly	Gly	Arg 110		Va1	

Пe	He	Ser 115		Asn	Ala	Va]	Asp 120		Asp	Ser	Phe	Tyr 125		Glu	Met	
Пe	G1n 130	Asp		Thr	Gln	Arg 135	Thr		Asp	Ile	Pro 140	Ala		Phe	Leu	
Leu 145	Gly	Arg	Asp	Gly	Tyr 150		Ile	Arg	Arg	Ser 155	Leu		ı Gln	His	Gly 160	
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Thr	Phe	Glu	Leu 180	Leu	G1n	Pro	Pro	Trp 185		Phe	Trp	•				
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				ggt Gly												96
				tca Ser												144
		Val	Leu	agc Ser	Leu	Gly		Ser	Ser	Phe	Val	Glu				192
				ttc Phe												240
gaa Glu	acc Thr	tac Tyr	aga Arg	aac Asn 85	tac Tyr	ttt Phe	ctg Leu	gga Gly	gat Asp 90	gac Asp	ggt Gly	gag Glu	cct Pro	ccg Pro 95	tgt Cys	288

														tgg Trp		336
			Gly											gga Gly		384
														gtg Val		432
									_		_	_	_	tcc Ser		480
											-			cac His 175	~ ~	528
														gcc Ala		576
														cct Pro		624
														tac Tyr		672
														aag Lys		720
			Gly											gtc Val 255		768
ggc Gly	att Ile	Leu	ttc Phe 260	acg Thr	ggc Gly	acc Thr	Lys	gac Asp 265	tta Leu	ctt Leu	aaa Lys	tct Ser	caa G1n 270	gtc Val	att Ile	816

gct Ala	gca Ala	gac Asp 275	Phe	aaa Lys	ctc Leu	aag Lys	act Thr 280	Va1	ggt Gly	tta Leu	ı tgç ı Trp	gag Glu 285	Ile	tat Tyr	agt Ser	864
		Val										His			ccg Pro	912
	Leu		ttt Phe								Met					960
			ctg Leu							He					Tyr	1008
tgg Trp	ttt Phe	ggt Gly	caa Gln 340	gca Ala	ttc Phe	ttc Phe	tat Tyr	ttt Phe 345	cag Gln	ggc Gly	aac Asn	tcc Ser	aac Asn 350	aac Asn	att Ile	1056
			gac Asp													1104
gaa Glu	atc Ile 370	cca Pro	gcc Ala	gtg Val	ctc Leu	ctg Leu 375	aca Thr	gcg Ala	ttt Phe	ggg Gly	acg Thr 380	tac Tyr	gca Ala	ggg Gly	cct Pro	1152
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agt Ser	ggt Gly	tca Ser	gca Ala	ctg Leu 405	agt Ser	cat His	gct Ala	tgc Cys	ttc Phe 410	tgc Cys	tac Tyr	gca Ala	ctg Leu	att Ile 415	tgt Cys	1248
tct Ser	att Ile	Pro	gtt Val 420	ttc Phe	acg Thr	tac Tyr	Пe	gtt Val 425	ttg Leu	gtg Val	aca Thr	tct Ser	ctg Leu 430	cgt Arg	tat Tyr	1296
cat His	Leu	ttt Phe 435	ata Ile	tgg Trp	agt Ser	Val	ttt Phe 440	tct Ser	cca Pro	aaa Lys	Leu	ctc Leu 445	tac Tyr	gag Glu	gga Gly	1344

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Ile	Ser	Lys	Gly	Ile 245		Glu	Ala	Arg	Phe 250		Tyr	Val	Phe	Va1 255	
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Va1 305	Leu	Ala	Phe	Ser	Leu 310	Leu	Ile	Gln	Thr	Leu 315	Met	Thr	Lys	Phe	Ile 320
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	370					375					Thr 380				
385				·	390					395	Ser				400
				405					410		Tyr			415	
			420					425			Thr		430		
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														gcc Ala			144
														cac His	tcg Ser		192
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														atc Ile			336
	Trp													acc Thr			384
														tcc Ser			432
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Gly	⁄ Ala	ı Arg	y Val	Ile 165		Thr	Asp	Thr	Trp 170		Met	: Lys	Val	Thr 175	Thr	
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			Gln					Pro					Pro		cag Gln	624
ctc Leu	ctc Leu 210	acc Thr	atc Ile	cgt Arg	gtg Val	gcc Ala 215	agc Ser	acc Thr	aac Asn	cct Pro	gct Ala 220	۷al	cag Gln	gcc Ala	ttt Phe	672
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Val Pro Phe His Leu Arg Arg Thr Ala Ala Thr Leu Leu Cys His Ser
Leu Leu Pro Leu Gly Tyr Tyr Val Gly Met Cys Leu Ala Ala Ser Glu
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                                        75
Lys Arg Leu His Ala Leu Ser Gln Ala Pro Glu Ala Trp Arg Leu Phe
Leu Leu Leu Ala Val Thr Leu Pro Ser Ile Ala Cys Ile Leu Ile Tyr
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Tyr Trp Ser Arg Asp Arg Trp Ala Cys His Pro Leu Ala Arg Thr Leu
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Ala Leu Tyr Ala Leu Pro Gln Ser Gly Trp Gln Ala Val Ala Ser Ser
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Val Asn Thr Glu Phe Arg Arg Ile Asp Lys Phe Ala Thr Gly Ala Pro
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Gly Ala Arg Val Ile Val Thr Asp Thr Trp Val Met Lys Val Thr Thr
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Tyr Arg Val His Val Ala Gln Gln Gln Asp Val His Leu Thr Val Thr
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Glu Ser Arg Gln His Glu Leu Ser Pro Asp Ser Asn Leu Pro Val Gln
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Asp 225		Trp	Leu	Asn	Ser 230		G1u	ı Tyr	Gly	Glu 235	Leu		Glu	Lys	Leu 240		
Arg	Ala	Pro	Пe	Arg 245	Arg	Ala	Ala	His	Va1 250	Val		His	Gln	Ser 255	Leu		
Gly	Asp	Leu	Phe 260	Leu	Glu	Xaa	Phe	Ala 265	Ser		۷a۱	Glu	Va7 270	Asn	Pro		
Ala	Tyr	Ser 275	۷a٦	Pro	Ser	Ser	G1n 280		Leu	Glu	Ala	Cys 285		Gly	Cys		
Met	G1n 290	Thr	Arg	Ala	Ser	Va1 295		Leu	۷a٦	Lys	Thr 300	Cys	Gln	Glu	Ala		
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Thr	Cys	Met	Gly	Lys 325	Trp	Phe	Ala	Ser	Arg 330	Gln	. Asp	Pro	Leu	Arg 335	Pro		
Asp	Thr	Trp	Leu 340	Ala	Ser	Arg	Val	Pro 345	Cys	Pro	Thr	Cys	Arg 350	Ala	Arg		
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acg Thr	tct Ser	gcc Ala	agg Arg 20	agc Ser	cag Gln	aag Lys	aca Thr	gaa Glu 25	cct Pro	cta Leu	agt Ser	ggc Gly	tct Ser 30	ggg Gly	gac Asp	96	õ
cag Gln	cca Pro	ctc Leu 35	ttc Phe	cgt Arg	gga Gly	gct Ala	gat Asp 40	cga Arg	tat Tyr	gac Asp	ttt Phe	gcc Ala 45	atc Ile	atg Met	ata Ile	144	1

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tac Tyr 65	Phe	tat Tyr	tto Phe	agt Ser	tac Tyr 70	Glu	gtt Val	cag Gln	cgg Arg	aca Thr	' Val	999 Gly	atg Met	tca Ser	cat His 80	240
gac Asp	cgg Arg	cat His	gtt Val	gct Ala 85	Ala	acg Thr	gca Ala	cat His	aac Asn 90	cca Pro	cag Gln	gga Gly	ttt Phe	cto Leu 95	ata Ile	288
gac Asp	acc Thr	tcc Ser	cag Gln 100	Gly	gtt Val	cgg Arg	ggc Gly	cag Gln 105	att Ile	aac Asn	ttc Phe	tct Ser	acc Thr 110	Gln	gag Glu	336
aca Thr	ggt Gly	ttt Phe 115	Tyr	cag Gln	ctt Leu	tgt Cys	cta Leu 120	agt Ser	aat Asn	cag G1n	cat His	aat Asn 125	His	ttc Phe	ggt Gly	384
tct Ser	gtg Val 130	caa G1n	gtg Val	tac Tyr	ctc Leu	aac Asn 135	ttt Phe	ggg Gly	gtc Val	ttc Phe	tat Tyr 140	gag Glu	999 Gly	cct Pro	gag Glu	432
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gca Ala	att Ile	gag Glu	gac Asp	ggc Gly 165	aca Thr	caa G1n	aag Lys	gtg Val	cag G1n 170	aac Asn	aat Asn	atc Ile	ttt Phe	cac His 175	atg Met	528
tgg Trp	cga Arg	tac Tyr	tac Tyr 180	aac Asn	ttt Phe	gcc Ala	cgg Arg	atg Met 185	agg Arg	aaa Lys	atg Met	gct Ala	gac Asp 190	ttt Phe	ttc Phe	576
ctt Leu	atc Ile	caa Gln 195	tca Ser	aac Asn	tat Tyr	Asn	tac Tyr 200	gtg Val	aac Asn	tgg Trp	tgg Trp	tcg Ser 205	aca Thr	gcc Ala	cag Gln	624
Ser	ctt Leu 210	gtt Val	att Ile	att Ile	Leu	tct Ser 215	999 Gly	atc Ile	ctg Leu	Gln	ctg Leu 220	tat Tyr	ttc Phe	ttg Leu	aag Lys	672

cgt																720
Arg	Leu	Phe	Asn	Val	Pro	Thr	Thr	Thr	Asp	Thr	Lys	Lys	Pro	Arg	Cys	
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														acc Thr		96
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														gac Asp		192
tgc Cys 65	gcc Ala	anc Xaa	gtg Val	cgg Arg	agg Arg 70	ctg Leu	gtg Val	ctc Leu	cgc Arg	ggc Gly 75	ctg Leu	gcc Ala	aac Asn	ctg Leu	gcc Ala 80	240
														ctc Leu 95		288
gcc Ala	atg Met	att Ile	ggc Gly 100	ggg Gly	ctg Leu	gac Asp	gac Asp	999 Gly 105	gac Asp	aac Asn	cct Pro	cac His	agc Ser 110	cca Pro	gtg Val	336

			ı Ala					ı Ala					Lei		gag Glu	384
		Asp					Leu					Ile			cgg Arg	432
	Phe					Lys					Thr				cgc Arg 160	480
					Asn					Gly						528
															ctg Leu	576
					acc Thr											624
atg Met	tgt Cys 210	ggc Gly	ccc Pro	aat Asn	ctg Leu	gca Ala 215	tgt Cys	gag Glu	gag Glu	ctc Leu	tca Ser 220	gct Ala	gct Ala	ttc Phe	cag Gln	672
					ggc Gly 230											720
acc Thr	acc Thr	tgc Cys	aag Lys	cac His 245	ctg Leu	atg Met	cac His	cat His	ttc Phe 250	cca Pro	gac Asp	ctg Leu	ctg Leu	ggc Gly 255	cgt Arg	768
ctc Leu	ctg Leu	acc Thr	acc Thr 260	tgc Cys	ctg Leu	ttc Phe	tac Tyr	ttc Phe 265	aag Lys	agc Ser	agc Ser	tgg Trp	gag Glu 270	aac Asn	gtc Val	816
cga Arg	gct Ala	gct Ala 275	gca Ala	ccc Pro	ctg Leu	Phe	acc Thr	999 Gly	ttc Phe	ctg Leu	gtg Val	ctg Leu	cac His	tcg Ser	gag Glu	864

Pro	agg Arg 290	g Glr	g cag n Glr	ı ccç ı Pro	g cag Glr	gtg Val 295	Asp	c cto Leo	ı Asp	cag Glr	cto Leu 300	ı Ile	t gog e Ala	gcç Ala	ctc Leu	912
cag Glr 305	116	ctg Lei	ctg Leu	aag Lys	gac Asp 310	Pro	gco Ala	ccc Pro	gaç Glu	gtg Val 315	Arg	acg Thr	g agg Arg	gct Ala	gct Ala 320	960
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Ala Ala Leu Cys 65 Ser Ala	Ala Cys Phe Leu 50 Ala Gly Met	Glu Thr Leu 35 Asp Xaa Cys	His 20 Ala Ser Val Pro Gly 100	5 Ser Glu Leu Arg Asp 85 Gly	Ser Leu Leu Arg 70 Lys Leu	Ala Leu Glu 55 Leu Val Asp Gly	Tyr Asn 40 Ser Val Arg Asp Leu	Glu 25 Ser Leu Leu Thr Gly 105	Asn Asn Ala Arg His 90 Asp	Gln Val Ala Gly 75 Gly Asn	Arg Ala Arg 60 Leu Pro	Val Asn 45 Gln Ala Gln His	Thr 30 Asp Lys Asn Leu	15 Thr Leu Asp Leu Leu 95 Pro	Thr Met Thr Ala 80 Thr	
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Gln	Asp	Pro 195		Ala	Thr	Val	Ala 200		Ala	Cys	Arg	Phe 205	Ala		Arg	
Met	Cys 210		Pro	Asn	Leu	Ala 215		Glu	Glu	Leu	Ser 220		Ala	Phe	Gln	
Lys 225	His	Leu	Gln	Glu	Gly 230		Ala	Leu	His	Phe 235		Glu	Phe	Leu	Asn 240	
Thr	Thr	Cys	Lys	His 245		Met	His	His	Phe 250	Pro	Asp	Leu	Leu	Gly 255	Arg	
Leu	Leu	Thr	Thr 260		Leu	Phe	Tyr	Phe 265		Ser	Ser	Trp	G1u 270	Asn	Val	
		275					. 280					285		Ser		
	290					295					300			Ala		
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aca (Thr	Leu	999 Gly 195	ctg Leu	caa G1n	caa G1n	Glu	aca Thr 200	aca Thr	gag Glu	ccc Pro	Met	aaa Lys 205	act Thr	gac Asp	agt Ser	624	
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Asp Pro Arg Asp Val Lys Asn Met Asn Thr Trp Leu Leu Phe Leu Pro
Leu Phe Pro Val Gln Val Gln Thr Leu Ile Val Val Ile Ile Gly Met
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                                        75
Leu Val Leu Leu Asp Phe Leu Gly Leu Val His Leu Gly Gln Leu
Leu Ile Phe His Ile Tyr Leu Lys Ala Lys Lys Met Thr Thr Phe Glu
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Tyr Leu Ile Asn Asn Arg Lys Glu Glu Ser Ser Lys His Gln Ala Val
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Arg Lys Asp Pro Tyr Val Gln Met Asp Lys Gly Val Leu Gln Gln Gly
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Asp Gly Asp Ser Lys Ala Gln Glu Ala Asp Asp Ala Pro Ser Thr Ser
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ggg Gly	tcc Ser	ccc Pro	ggt Gly 20	Gly	ctc Leu	acc Thr	ago Ser	cto Leu 25	Gin	ıcag Glr	ıcaç ıGlr	g aag 1 Lys	cag Gln 30	ı Arg	ctg Leu	96
atc Ile	gag Glu	tcc Ser 35	ctc Leu	cgg Arg	aac Asn	tca Ser	cac His 40	Ser	agt Ser	ata Ile	gcc Ala	gaa Glu 45	Пe	cag Gln	aaa Lys	144
gat Asp	gtg Val 50	gaa Glu	tac Tyr	aga Arg	ttg Leu	cca Pro 55	ttc Phe	acc Thr	ata Ile	aac Asn	aac Asn 60		aca Thr	att Ile	aac Asn	192
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agt Ser	gtt Val	tat Tyr	cca Pro	cca Pro 85	ata Ile	cga Arg	cat His	cac His	tta Leu 90	atg Met	gat Asp	aaa Lys	caa Gln	gga Gly 95	gtg Val	288
tat Tyr	gtt Val	acc Thr	tct Ser 100	cca Pro	tta Leu	gta Val	aac Asn	aat Asn 105	ttt Phe	aca Thr	atg Met	cac His	tca Ser 110	gat Asp	ctt Leu	336
gga Gly	aaa Lys	att Ile 115	att Ile	cag Gln	agt Ser	Leu	ttg Leu 120	gat Asp	gag Glu	ttt Phe	tgg Trp	aag Lys 125	aat Asn	cct Pro	cca Pro	384
gtt Val	tta Leu 130	gct Ala	cct Pro	act Thr	tca Ser	aca Thr 135	gca Ala	ttt Phe	cct Pro	tat Tyr	cta Leu 140	tac Tyr	agt Ser	aac Asn	cca Pro	432
agt g Ser (145	999 Gly 1	atg Met	tct Ser	Pro	tat Tyr 150	gct Ala:	tct Ser	cag Gln	Gly	ttt Phe 155	cca Pro	ttt Phe	ctt Leu	cct Pro	cca Pro 160	480
tat d	cct (cca (caa	gaa	gca	aac a	agg	agt	atc	act	tct	tta	tct	gtt	gct	528

Tyr	Pro	Pro	Gln	Glu 165		Asn	Arg	Ser	` Ile 170		· Ser	Leu	Ser	Val 175	Ala	
				Ser					His					Pro	gcc Ala	576
			Phe												aca Thr	624
gtg Val	gat Asp 210	gct Ala	tca Ser	ata Ile	ccg Pro	aca Thr 215	agc Ser	caa Gln	aat Asn	ggt Gly	ttt Phe 220	999 Gly	tac Tyr	aag Lys	atg Met	672
cca Pro 225	gat Asp	gtc Val	cct Pro	gat Asp	gca Ala 230	ttt Phe	cca Pro	gaa Glu	ctc Leu	tca Ser 235	gaa Glu	cta Leu	agt Ser	gtg Val	tca Ser 240	720
caa G1n	ctc Leu	aca Thr	gat Asp	atg Met 245	aat Asn	gaa Glu	caa Gln	gag Glu	gag Glu 250	gta Val	tta Leu	cta Leu	gaa Glu	cag Gln 255	ttt Phe	768
				caa G1n												816
				gag Glu		Leu										864
Ser	ttg Leu 290	gaa Glu	gcc Ala	aaa Lys	aga Arg	caa Gln 295	act Thr	gtt Val	tta Leu	gat Asp	aag Lys 300	tat Tyr	gaa Glu	tta Leu	ctt Leu	912
aca Shr 305	cag Gln	atg Met	aag Lys	tcc Ser	act Thr 310	ttc Phe	gaa Glu	aag Lys	Lys	ațg Met 315	caa G1n	agg Arg	cag G1n	cat His	gaa Glu 320	960
ett eu	agt Ser	gag Glu	Ser	tgt Cys 325	agt Ser	gca Ala:	agt Ser	Ala	ctt Leu 330	cag Gln	gca Ala	aga Arg	ttg Leu	aaa Lys 335	gta Val	1008
jct ·	gca	cat	gaa	gct	gag	gaa (gaa	tct	gat	aat	att	gca	gaa	gac	ttc	1056

Ala	a Ala	a His	s G](340	u Ala)	a Glu	ı Glu	ı Glu	345) Asr	n Ile	e Ala	a G1u 350) Phe		
ttg Lei	gag Glu	gga Gly 355	/ Lys	j atg Met	gaa :Glu	a ata ı Ile	gat Asp 360) Asp	ttt Phe	cto Lei	agt Ser	ago Ser 365	Phe	ato Met	g gaa : Glu	11	04
aag Lys	aga Arg 370	Thr	att Ile	tgc Cys	cac His	tgt Cys 375	Arg	aga Arg	gco Ala	aag Lys	gaa Glu 380	ı Glu	aaa Lys	ctt Leu	cag Gln	119	52
cag G1n 385	Ala	ata Ile	gca Ala	atg Met	cac His 390	Ser	caa G1n	ttt Phe	cat His	gct Ala 395	Pro	cta Leu	tag *	*		119	94
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Gly	Ser	Pro	G1y 20	Gly	Leu	Thr	Ser	Leu 25	Gln	Gln	Gln	Lys	G1n 30	Arg	Leu		
Пe	Glu	Ser 35	Leu	Arg	Asn	Ser	His 40	Ser	Ser	Ile	Ala	G1u 45	Ile	Gln	Lys		
٩sp	Val 50	Glu	Tyr	Arg	Leu	Pro 55	Phe	Thr	He	Asn	Asn 60	Leu	Thr	Ile	Asn		
Ile 65	Asn	Ile	Leu	Leu	Pro 70	Pro	Gln	Phe	Pro	G1n 75		Lys	Pro	Val	Ile 80		
Ser	Val	Tyr	Pro	Pro 85	Пe	Arg	His	His	Leu 90	Met	Asp	Lys	Gln	G1 <i>y</i> 95	Val		
Гуr	Val	Thr	Ser 100	Pro	Leu	Val	Asn	Asn 105	Phe	Thr	Met	His	Ser 110	Asp	Leu		
Sly	Lys	Ile 115	Ile	Gln	Ser		Leu 120		Glu	Phe	Trp	Lys 125	Asn	Pro	Pro		
/al	Leu 130	Ala	Pro	Thr	Ser			Phe	Pro	Tyr	Leu 140	Tyr	Ser	Asn	Pro		
er .45	Gly	Met	Ser	Pro	Tyr 150		Ser	Gln		Phe 155		Phe	Leu	Pro	Pro 160		
	Pro	Pro	Gln	Glu 165		Asn	Arg				Ser	Leu	Ser	Val 175	Ala		

Thr	Val			Ser	Thr	Thr			Thr	Thr	` Ala			Ala		
Pro			Gly	Val	Leu		Asn		Pro	Leu		He		Thr		
210					215					220		-	_			
				230					235					240		
			245					250					255			
Thr	Leu	Pro 260	G1n	Leu	Lys	Gln	Ile 265	Ile	Thr	Asp	Lys			Leu		
	275					280					285					
290					295					300						
				310					315					320		
			325					330					335			
		340					345					350				
	355					360					365					
370					375					380		Lys	Leu	Gln		
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cgg	aac	agc	aag	aag	agg	ccg	gcc	agc	cct	tcc	cac	aat	ggc	agc		96
	Asp 210 Asp 210 Asp Leu 290 Gln Ser Ala Glu Arg 370 Ala <22 <22 <22 <22 <22 <42 gcg Ala	Arg Thr Ser Glu Ala His Glu Gly 355 Arg Thr 370 Ala Ile <210> <211> <212> <213> <220> <221> <222> <400> gcg gcg Ala Ala	180 Pro Ser Phe 195 Asp Ala Ser 210 Asp Val Pro Leu Thr Asp Leu Thr Asp Thr Leu Pro 260 Lys Ser Ile 275 Leu Glu Ala 290 Gln Met Lys Ser Glu Ser Ala His Glu 340 Glu Gly Lys 355 Arg Thr Ile 370 Ala Ile Ala <210> 281 <212> DNA <213> Homo <220> <221> CDS <222> (1) <400> 281 gcg gcg caa Ala Ala Gln	180 a Pro Ser Phe Gly 195 Asp Ala Ser Ile 210 a Asp Val Pro Asp b Leu Thr Asp Met 245 Thr Leu Pro Gln 260 Lys Ser Ile Glu 275 Leu Glu Ala Lys 290 Gln Met Lys Ser Ser Glu Ser Cys 325 Ala His Glu Ala 340 Glu Gly Lys Met 355 Arg Thr Ile Cys 370 Ala Ile Ala Met <210> 281 <21> 579 <212> DNA <213> Homo sap <220> <221> CDS <222> (1)(5) <400> 281 gcg gcg caa att Ala Ala Gln Ile 5	180 A Pro Ser Phe Gly Val 195 Asp Ala Ser Ile Pro 210 Asp Val Pro Asp Ala 230 Leu Thr Asp Met Asn 245 Thr Leu Pro Gln Leu 260 Lys Ser Ile Glu Glu 275 Leu Glu Ala Lys Arg 290 Gln Met Lys Ser Thr 310 Ser Glu Ser Cys Ser 325 Ala His Glu Ala Glu 340 Glu Gly Lys Met Glu 355 Arg Thr Ile Cys His 370 Ala Ile Ala Met His 390 <210> 281 <211> 579 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)(579) <400> 281 gcg gcg caa att cca Ala Ala Gln Ile Pro 5	180 A Pro Ser Phe Gly Val Leu 195 Asp Ala Ser Ile Pro Thr 210 215 Asp Val Pro Asp Ala Phe 230 Leu Thr Asp Met Asn Glu 245 Thr Leu Pro Gln Leu Lys 260 Lys Ser Ile Glu Glu Leu 275 Leu Glu Ala Lys Arg Gln 290 295 Gln Met Lys Ser Thr Phe 310 Ser Glu Ser Cys Ser Ala 325 Ala His Glu Ala Glu Glu 340 Glu Gly Lys Met Glu Ile 355 Arg Thr Ile Cys His Cys 370 375 Ala Ile Ala Met His Ser 390 <210> 281 <211> 579 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)(579) <400> 281 gcg gcg caa att cca att Ala Ala Gln Ile Pro Ile 5	180 a Pro Ser Phe Gly Val Leu Ser 195 200 Asp Ala Ser Ile Pro Thr Ser 210 215 a Asp Val Pro Asp Ala Phe Pro 230 b Leu Thr Asp Met Asn Glu Gln 245 a Thr Leu Pro Gln Leu Lys Gln 260 b Lys Ser Ile Glu Glu Leu Ala 275 280 b Leu Glu Ala Lys Arg Gln Thr 290 295 c Gln Met Lys Ser Thr Phe Glu 310 c Ser Glu Ser Cys Ser Ala Ser 325 b Ala His Glu Ala Glu Glu Glu 340 c Glu Gly Lys Met Glu Ile Asp 355 360 c Arg Thr Ile Cys His Cys Arg 370 c Ala Ile Ala Met His Ser Gln 390 c <210> 281 c <210> 281 c <21> DNA c <213> Homo sapiens c <220> c <221> CDS c <222> (1)(579) c <400> 281 gcg gcg caa att cca att gtg Ala Ala Gln Ile Pro Ile Val 5	180	180	180	180	180	180	180	Pro Ser Phe Gly Val Leu Ser Asn Leu Pro Leu Pro Ile Pro Thr 195	180

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			Gly			gcc Ala							Ser		tcc Ser	144
agc Ser	ttt Phe 50	gcg Ala	cag Gln	ggt Gly	atc Ile	agc Ser 55	atg Met	gaa Glu	gcc Ala	atg Met	agt Ser 60	gag Glu	aat Asn	aaa Lys	atg Met	192
						aca Thr										240
						aac Asn										288
						aga Arg										336
						ccg Pro			-		-					384
agt Ser	att Ile 130	gat Asp	gct Ala	cct Pro	cca Pro	tcc Ser 135	ttt Phe	aag Lys	cca Pro	gct Ala	aag Lys 140	aag Lys	tat Tyr	tct Ser	gat Asp	432
						aac Asn										480
ttc Phe	agc Ser	acc Thr	Пe	gaa Glu 165	gag Glu	ttt Phe	tcc Ser	Tyr	att Ile 170	cgg Arg	agg Arg	ctg Leu	ccc Pro	tct Ser 175	gac Asp	528
jtc /al	gtc Val	Thr	ggc Gly 180	tac Tyr	ctg Leu	gcc Ala	Leu	agg Arg 185	aag Lys	gcc Ala	acg Thr	agc Ser	atc Ile 190	gtt Val	ccc Pro	576
ga																579

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Ser Gly Gly Gly Tyr Gly Ala Ser Lys Lys Lys Ala Ser Ala Ser
Ser Phe Ala Gln Gly Ile Ser Met Glu Ala Met Ser Glu Asn Lys Met
Val Pro Ser Glu Phe Ser Thr Gly Pro Val Glu Lys Ala Ala Lys Pro
Leu Pro Phe Lys Asp Pro Asn Phe Val His Ser Gly His Gly Gly Ala
Val Ala Gly Lys Lys Asn Arg Thr Trp Lys Asn Leu Lys Gln Ile Leu
                                105
Ala Ser Glu Arg Ala Leu Pro Trp Gln Leu Asn Asp Pro Asn Tyr Phe
Ser Ile Asp Ala Pro Pro Ser Phe Lys Pro Ala Lys Lys Tyr Ser Asp
                        135
                                            140
Val Ser Gly Leu Leu Ala Asn Tyr Thr Asp Pro Gln Ser Lys Leu Arg
                                        155
Phe Ser Thr Ile Glu Glu Phe Ser Tyr Ile Arg Arg Leu Pro Ser Asp
                165
                                    170
Val Val Thr Gly Tyr Leu Ala Leu Arg Lys Ala Thr Ser Ile Val Pro
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									tct Ser				Gly				144
									aaa Lys			Lys					192
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att Ile	ccc Pro	cag Gln	aaa Lys	tcc Ser 85	tcc Ser	cat His	gct Ala	gtt Val	tgt Cys 90	aac Asn	gct Ala	caa G1n	cat His	gat Asp 95	ctt Leu		288
									tca Ser								336
									aca Thr								384
					Leu	Leu	Leu	Ser	aaa Lys	Leu		Tyr					432
aaa Lys 145	aag Lys	gag Glu	tat Tyr	Glu	gat Asp 150	gct Ala	gaa Glu	aat Asn	act Thr	tca Ser 155	act Thr	cag Gln	tcc Ser	aaa Lys	gtt Val 160		480
atg Met	aat Asn	aaa Lys	aaa Lys	gat Asp 165	aaa Lys	aga Arg	aag Lys	aat Asn	cat His 170	cag Gln	gga G1y	aaa Lys	gac Asp	aga Arg 175	cct Pro	:	528

ctc Leu	aca Thr	gta Val	tça Ser 180	cta Leu	aaa Lys	gat Asp	ttt Phe	cat His 185	Ser	gaa Glu	gat Asp	cac His	att Ile 190	agt Ser	aaa Lys	576
							aaa Lys 200									624
							gct Ala									672
							tat Tyr									720
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		35					40					45	_		Lys
	50					55					60				Glu
65					70					75				_	Lys 80
				85					90					95	Leu
			100		Val			105					110		
		115			Asp		120					125			
	130				Leu	135					140				
145					Asp 150					155				_	160
				165	Lys				170					175	
			180		Lys			185					190		•
		195			Val		200					205			
	210				Lys	215					220				
225					A1a 230					235					240
				245	Leu				250			·	_	255	
			260		Asp			265					270		
		275			Leu		280					285			
	290					295					G1n 300	Gly	G1y	Arg	Lys
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				Ser					Gln					Cys	ccc Pro	96	5
tgg Trp	agc Ser	cat His 35	Arg	cgg Arg	cat His	gtg Val	atg Met 40	cag Gln	cag G1n	gga Gly	gaa Glu	cag Gln 45	cag Gln	cag G1n	atc Ile	144	ļ
cca Pro	gac Asp 50	ccc Pro	tgc Cys	agg Arg	ctt Leu	tca Ser 55	act Thr	gct Ala	act Thr	tta Leu	aaa Lys 60	tgt Cys	ttg Leu	caa Gln	gcc	192	•
												gag Glu				240	,
												ata Ile				288	,
												gtc Val				336	
												tcg Ser 125				384	
gg Arg	ata Ile 130	acc Thr	ggc Gly	gca Ala	gct Ala	ttc Phe 135	ttc Phe	tct Ser	gag Glu	ctc Leu	atg Met 140	aag Lys	gaa Glu	cca Pro	atc Ile	432	
tt	tgg	aag	cat	9 99	aat	ctg	cga	aat	gtg	ctg	atc	ttg	atg	gat	caa	480	

Leu 145	Trp	Lys	His	Gly	/ Asr 150		ı Arg	Asr	ı Val	Leu 155		e Leu	Met	: Asp	Gln 160		
agt Ser	gcc Ala	tgg Trp	gac Asp	tcc Ser 165	Asn	gcc Ala	act Thr	ctg Leu	agg Arg 170	Gln	atg Met	gcc : Ala	atc Ile	cga Arg 175	ggg Gly	√52	:8
ctc Leu	ggc Gly	aac Asn	aca Thr 180	Ala	tcc Ser	999 Gly	gct Ala	cct Pro 185	His	aag Lys	gtg Val	aag Lys	aaa Lys 190	His	aag Lys	57	6
cag G1n	tta Leu	atg Met 195	Leu	gaa Glu	tct Ser	atc Ile	atc Ile 200	aga Arg	ggc Gly	ctg Leu	tat Tyr	cac His 205	cta Leu	gct Ala	cgc Arg	62	4
act Thr	gaa Glu 210	gtc Val	gtc Val	tgt Cys	gaa Glu	agc Ser 215	ttg Leu	aag Lys	gct Ala	cta Leu	aaa Lys 220	aaa Lys	atc Ile	ctg Leu	gag G1u	67	2
ctg Leu 225	ctg Leu	aca Thr	gac Asp	cga Arg	gac Asp 230	gtg Val	agc Ser	ttc Phe	tac Tyr	ttc Phe 235	aag Lys	gaa Glu	ata Ile	gtg Val	ctg Leu 240	720)
caa Gln	aca Thr	agg Arg	acc Thr	ttc Phe 245	ttt Phe	gaa Glu	gat Asp	gag Glu	cag G1n 250	gat Asp	gat Asp	gtg Val	aga Arg	ttg Leu 255	act Thr	768	3
gcc Ala	atc Ile	ttc Phe	tta Leu 260	ttt Phe	gag Glu	gac Asp	ctg Leu	gca Ala 265	ccc Pro	cta Leu	aca Thr	gga Gly	aga Arg 270	agg Arg	tgg Trp	816	Š
aag _ys	att Ile	ttt Phe 275	ttt Phe	gct Ala	gaa Glu	gaa Glu	ata Ile 280	aaa Lys	aag Lys	agc Ser	ctg Leu	att Ile 285	tca Ser	ttc Phe	ctt Leu	864	ļ
etg Leu	cac His 290	ctt Leu	tgg Trp	gat Asp	ccc Pro	aac Asn 295	ccc Pro	aag Lys	att Ile	Gly	gtt Val 300	gct Ala	tgc Cys	cgt Arg	gat Asp	912	•
tc /al 805	ttg Leu	atg Met	gtc Val	Cys	att Ile 310	ccc Pro	ttt Phe	ttg Leu	Gly	ctc Leu 315	cag G1n	gag Glu	ctc Leu	tat Tyr	999 Gly 320	960	
ta	tta	gac	cgt	ctc	ctt	gat	cag	gat	cta	cca	agg	gcc	agg	gat	ttc	1008	

Val	Leu	Asp	Arg	Leu 325	Leu	Asp	Gln	Asp	Leu 330		Arg	Ala	Arg	Asp 335		
			ttc Phe 340						Lys							1056
			cac His													1104
			agt Ser													1152
			caa G1n													1200
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	cct Pro	-	taa *													1308
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1			Val	5					10					15		
			20					25					30			
пр		35	Arg .	mı y	1115		мет 40	uin	um	ыіу	GIU	45	uin	uin	116	

Pro	Asp 50	Pro	Cys	Arg	, Leu	Ser 55	Thr	` Alá	a Thr	· Lei	ı Lys 60	Cys	Lei	G1r	1 A I
G1n 65	Ala	Met	: Arg	ı Glu	Gly 70	Leu	ı Ala	Lys	G]L	ı Ser 75	· Asp	G]ı	ı Gly	Asp	Ası 80
				85					90				e Gly	95	ŭ
			100					105	•				Ile 110		
-		115					120					125			
Arg	Ile 130		Gly	Ala	Ala	Phe 135		Ser	· Glu	ı Leı	Met 140		Glu	Pro	Πe
Leu 145		Lys	His	Gly	Asn 150		Arg	Asn	Va1	Leu 155		Leu	Met	Asp	G1r 160
				165					170				He	175	•
			180					185					Lys 190		
		195					200					205			
	210					215					220		Ile		
225					230					235			Ile		240
				245					250				Arg	255	
Ala	Ile	Phe	Leu 260	Phe	Glu	Asp	Leu	Ala 265		Leu	Thr	Gly	Arg 270	Arg	Trp
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	290					295					300		Cys		
Va1 305	Leu	Met	Val	Cys	Ile 310	Pro	Phe	Leu	Gly	Leu 315	Gln	Glu	Leu	Tyr	G1y 320
Val	Leu	Asp	Arg	Leu 325	Leu	Asp	Gln	Asp			Arg		Arg	Asp 335	
Tyr	Arg	Gln	Phe 340	Cys	Val	Lys	Leu	A1a 345	Lys	Lys	Asn	Gln	G1u 350	Пe	Leu
Trp	Пe	Leu 355	His	Thr	His	Ser	Phe 360	Thr	Phe	Phe	Thr	Ser 365	Thr	Trp	Glu
	Ile 370	Arg	Ser	Ala		Va1 375	Lys	Leu	Thr	Asp	A1a 380		Val	Leu	Asn
Leu 385	Thr	Ser	G1n	Tyr	Va1 390	Glu	Leu	Leu	Asp	Arg 395	G1u	Gln	Leu	Thr	Thr 400

Arg	Leu	Gln	Ala	Leu 405		Gln	Asp	Pro	Cys 410		Ser	· Val	Gln	Arg 415		
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a to a			287													
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tgg Trp	tcg Ser	tcg Ser	gcc Ala 20	tct Ser	gca Ala	ccc Pro	ccg Pro	ccg Pro 25	cgg Arg	ggg Gly	ttc Phe	agc Ser	gcg Ala 30	atc Ile	tcc Ser	96
				999 Gly												144
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ro 65	cag G1n	gag Glu	aac Asn	gtg Val	gtg Val 70	gcc Ala	gat Asp	atc Ile	cag Gln	atc Ile 75	gtg Val	gtg Val	gac Asp	aag Lys	agc Ser 80	240
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gga Gly	gcc Ala	acg Thr	, Asb	acg Thr	gct Ala	gtg Val	ttt Phe 120	Asp	gtc Val	cgg Arg	ıctg Leu	agt Ser 125	Gly	aag Lys	acc Thr	384
aag Lys	aca Thr 130	Val	cct Pro	gga Gly	tac Tyr	ctt Leu 135	cga Arg	ata Ile	999 Gly	gac Asp	atg Met 140	ggc Gly	ggc	ttt Phe	gcc Ala	432
atc Ile 145	tgg Trp	tgc Cys	aag Lys	aag Lys	gcc Ala 150	aag Lys	gcc Ala	ccg Pro	agg Arg	cca Pro 155	Val	ccc Pro	aag Lys	ccc Pro	cga Arg 160	480
ggt Gly	ctc Leu	agc Ser	cgg Arg	gac Asp 165	atg Met	cag Gln	ggc Gly	ctc Leu	tct Ser 170	ctg Leu	gat Asp	gca Ala	gcc Ala	agc Ser 175	cag Gln	528
cca Pro	agt Ser	aag Lys	ggc Gly 180	ggc Gly	ctc Leu	ctg Leu	gag Glu	cgg Arg 185	aca Thr	gcg Ala	tca Ser	agg Arg	ctg Leu 190	ggc Gly	tct Ser	576
cgg Arg	gca Ala	tcc Ser 195	act Thr	ctg Leu	cgg Arg	agg Arg	aat Asn 200	gac Asp	tcc Ser	atc Ile	tac Tyr	gag Glu 205	gcc. Ala	tcc Ser	agc Ser	624
Leu	tat Tyr 210	ggc Gly	atc Ile	tca Ser	gcc Ala	atg Met 215	gat Asp	999 Gly	gtt Val	ccc Pro	ttc Phe 220	aca Thr	ctc Leu	cac His	cca Pro	672
cga Arg 225	ttt Phe	gag Glu	ggc Gly	aag Lys	agc Ser 230	tgc Cys	agc Ser	ccc Pro	ctg Leu	gcc Ala 235	ttc Phe	tct Ser	gct Ala	ttt Phe	999 Gly 240	720
gac Asp	ctg Leu	acc Thr	IJе	aag Lys 245	tct Ser	ctg Leu	gcg Ala	Asp	att Ile 250	gag Glu	gag Glu	gag Glu	tat Tyr	aac Asn 255	tac Tyr	768
ggc Gly	ttc Phe	Val	gtg Val 260	gag Glu	aag Lys	acc Thr	Ala	gct Ala 265	gcc Ala	cgc Arg	ctg Leu	Pro	ccc Pro 270	agc Ser	gtc Val	816
tca : Ser	tag *															822

<210> 288 <211> 273 <212> PRT <213> Homo sapiens

<400> 288

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				Glu											gcc Ala	96
tgt Cys	atc Ile	aac Asn 35	tct Ser	ggt Gly	atg Met	gac Asp	aca Thr 40	gct Ala	tct Ser	agt Ser	gtt Val	gct Ala 45	ttg Leu	gat Asp	ctt Leu	144
						gtg Val 55									gca. Ala	192
						ttg Leu										240
gct Ala	gtt Val	caa G1n	tct Ser	aca Thr 85	ata Ile	aat Asn	cat His	gtg Val	aaa Lys 90	gaa Glu	gaa Glu	cgt Arg	cca Pro	gaa Glu 95	aaa Lys	288
ata Ile	cca Pro	gat Asp	tta Leu 100	aaa Lys	tta Leu	ttg Leu	gta Val	gag Glu 105	aag Lys	aaa Lys	ttt Phe	ttg Leu	gct Ala 110	tta Leu	cag Gln	336
agc Ser	aag Lys	aat Asn 115	tct Ser	gat Asp	gca Ala	gac Asp	ttt Phe 120	caa Gln	aat Asn	aat Asn	gaa Glu	aaa Lys 125	ttt Phe	gta Val	cag Gln	384
ttt	aaa	caa	cag	ctg	aaa	gaa	cta	aag	aag	caa	tgt	ggt	ctt	caa	gct	432

Phe	Lys 130		G]n	Leu	Lys	G1u 135		Lys	Lys	G]n	1, Cys 140		/ Leu	Glr	ı Ala	
gac Asp 145	Arç	gaa Glu	gct Ala	gac Asp	gga Gly 150	aca Thr	gaa Glu	gga Gly	gtg Val	gat Asp 155	Glu	gat Asp	ata Ile	att	gtg Val 160	480
					Asn					Пe					atg Met	528
				Lys					Gly						gac Asp	576
gcc Ala	att Ile	gtt Val 195	cgc Arg	atg Met	att Ile	gag Glu	tcc Ser 200	agg Arg	caa G1n	aag Lys	cgg Arg	aag Lys 205	Lys	aag Lys	gcc Ala	624
tat Tyr	tgc Cys 210	Pro	caa G1n	att Ile	ggc Gly	tgt Cys 215	agc Ser	cac His	acg Thr	gat Asp	ata Ile 220	Arg	aag Lys	tca Ser	gat Asp	672
ett Leu 225	atc Ile	cag Gln	gat Asp	gaa Glu	gca Ala 230	ctt Leu	aga Arg	agg Arg	gca Ala	att Ile 235	gag Glu	aac Asn	cat His	aac Asn	aag Lys 240	720
		cat His					tag *									7 4 4
	<' _c	210> 211> 212> 213>	247 PRT	sap	oiens											
let		<004		Sar	Sar	Sar	Λcn	Son	G1v	San	Thn	Clv	Phe	Tla	202	
1				5					10					15		
			20					25					Phe 30			
ys	Ile	Asn 35	Ser	Gly	Met		Thr . 40	Ala	Ser	Ser	Val	A1a 45	Leu	Asp	Leu	

15

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Val Glu Ser Gln Thr Glu Val Ser Ser Glu Tyr Ser Met Asp Lys Ala
                         55
 Met Val Glu Phe Ala Thr Leu Asp Arg Gln Leu Asn His Tyr Val Lys
                     70 .
 Ala Val Gln Ser Thr Ile Asn His Val Lys Glu Glu Arg Pro Glu Lys
 Ile Pro Asp Leu Lys Leu Leu Val Glu Lys Lys Phe Leu Ala Leu Gln
             100
                                 105
 Ser Lys Asn Ser Asp Ala Asp Phe Gln Asn Asn Glu Lys Phe Val Gln
                             120
                                                 125
 Phe Lys Gln Gln Leu Lys Glu Leu Lys Lys Gln Cys Gly Leu Gln Ala
                         135
 Asp Arg Glu Ala Asp Gly Thr Glu Gly Val Asp Glu Asp Ile Ile Val
                     150
                                        155
 Thr Gln Ser Gln Thr Asn Phe Thr Cys Pro Ile Thr Lys Glu Glu Met
                165
                                   170
Lys Lys Pro Val Lys Asn Lys Val Cys Gly His Thr Tyr Glu Glu Asp
                                185
Ala Ile Val Arg Met Ile Glu Ser Arg Gln Lys Arg Lys Lys Ala
                            200
                                                 205
Tyr Cys Pro Gln Ile Gly Cys Ser His Thr Asp Ile Arg Lys Ser Asp
                        215
                                            220
Leu Ile Gln Asp Glu Ala Leu Arg Arg Ala Ile Glu Asn His Asn Lys
                    230
                                        235
Lys Arg His Arg His Ser Glu
                245
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      <221> misc_feature
      <222> (1)...(957)
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Met Ala Glu His Ala Gly Pro Arg Leu Pro Leu Val Leu Lys Thr Leu
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gcc Ala	ttc Phe	ctg Leu 35	Ala	gag Glu	ctg Leu	ctg Leu	aac Asn 40	Ser	aac Asn	gtg Val	gcc Ala	aac Asn 45	Asp	ctc Leu	atg Met	144
ctc Leu	ttg Leu 50	gac Asp	tcg Ser	ctg Leu	ctg Leu	gag Glu 55	agc Ser	ctg Leu	gcg Ala	gct Ala	cgc Arg 60	Gln	aag Lys	gac Asp	aca Thr	192
tgc Cys 65	gcc Ala	anc Xaa	gtg Val	cgg Arg	agg Arg 70	ctg Leu	gtg Val	ctc Leu	cgc Arg	ggc Gly 75	Leu	gcc Ala	aac Asn	ctg Leu	gcc Ala 80	240
tcc Ser	ggc Gly	tgc Cys	cct Pro	gac Asp 85	aag Lys	gtg Val	cga Arg	acc Thr	cac His 90	ggc Gly	ccc Pro	cag Gln	ctc Leu	ctc Leu 95	aca Thr	288
gcc Ala	atg Met	att Ile	ggc Gly 100	999 Gly	ctg Leu	gac Asp	gac Asp	999 Gly 105	gac Asp	aac Asn	cct Pro	cac His	agc Ser 110	cca Pro	gtg Val	336
gcc Ala	ctg Leu	gag Glu 115	gcc Ala	atg Met	ctg Leu	ggc Gly	ctt Leu 120	gcg Ala	agg Arg	ctg Leu	gtg Val	cac His 125	ctg Leu	gtg Val	gag Glu	384
tcc Ser	tgg Trp 130	gac Asp	ctg Leu	cgc Arg	tca Ser	999 Gly 135	ctg Leu	ctg Leu	cac His	gtg Val	gcc Ala 140	atc Ile	cgc Arg	atc Ile	cgg Arg	432
oct Pro 145	ttc Phe	ttc Phe	gac Asp	agt Ser	gag Glu 150	aag Lys	atg Met	gag Glu	ttc Phe	cgg Arg 155	acg Thr	gca Ala	tct Ser	atc Ile	dgc Arg 160	480
etc .eu	ttt Phe	999 Gly	cac His	ctt Leu 165	aac Asn	aag Lys	gtc Val	tgc Cys	cac His 170	gga Gly	gac Asp	tgt Cys	gag Glu	gac Asp 175	gtc Val	528
tc he	ctg Leu	Asp	cag G1n 180	gtg Val	gtg Val	ggc (Gly (Gly	ctg Leu 185	gcg Ala	ccc Pro	ctg Leu	ctg Leu	ctg Leu 190	cac His	ctg Leu	576

		acc Thr				Ala		cgc Arg	624
		ctg Leu							672
		ggc Gly 230							720
		ctg Leu							768
		ctg Leu							816
		ctg Leu							864
		cag Gln							912
		ccc Pro 310					tag *		957

<210> 292

<211> 318

<212> PRT

<213> Homo sapiens

<220>

<221> VARIANT

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Ala	Суs	Thr	His 20	Ser	Ser	Ala	Tyr	Glu 25	Asn	Gln	Arg	Val	Thr 30	Thr	Thr
Ala	Phe	Leu 35	Ala	Glu	Leu	Leu	Asn 40	Ser	Asn	Val	Ala	Asn 45	Asp	Leu	Met
Leu	Leu 50	Asp	Ser	Leu	Leu	G1u 55	Ser	Leu	Ala	Ala	Arg 60	GIn	Lys	Asp	Thr
Cys 65	Ala	Xaa	Val	Arg	Arg 70	Leu	Val	Leu	Arg	Gly 75	Leu	Ala	Asn	Leu	A1a 80
				85					90	Gly				95	
			100				·	105	•	Asn			110		
		115					120			Leu		125			
	130					135				Val	140				_
145					150					Arg 155					160
				165					170	Gly	4 10			175	
Phe	Leu	Asp	Gln 180	Val	Val	Gly	Gly	Leu 185	Ala	Pro	Leu	Leu	Leu 190	His	Leu
		195					200			Cys		205			_
	210					215				Leu	220				
225					230					Phe 235					240
				245					250	Pro				255	-
Leu	Leu	Thr	Thr 260	Cys	Leu	Phe	Tyr	Phe 265	Lys	Ser	Ser	Trp	G1u 270	Asn	Val
Arg	Ala	Ala 275	Ala	Pro	Leu	Phe	Thr 280	Gly	Phe	Leu	Val	Leu 285	His	Ser	Glu
Pro	Arg 290	Gln	Gln	Pro	Gln	Val 295	Asp	Leu	Asp	Gln	Leu 300	Ile	Ala	Gly	G1u
His 305	Pro	Ser	Thr	Gly	Pro 310	Leu	Arg	Trp	Ala	Leu 315	Leu	Thr	Leu		

<210> 293 <211> 1107

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				Pro					Phe					Ile	agg Arg	96
gat Asp	atc Ile	ctg Leu 35	gac Asp	atg Met	aag Lys	gag Glu	tcc Ser 40	cgc Arg	cag Gln	gtg Val	cca Pro	ggt Gly 45	Val	ttt Phe	ttg Leu	144
														gtc Val		192
gga Gly 65	gtg Val	aga Arg	gaa Glu	aga Arg	gat Asp 70	gct Ala	ttc Phe	tac Tyr	agt Ser	tat Tyr 75	gga Gly	gtg Val	gat Asp	gac Asp	agc Ser 80	240
														gag Glu 95		288
gta /al	tca Ser	gct Ala	gct Ala 100	cca Pro	agt Ser	gca Ala	gca Ala	aga Arg 105	gag Glu	ctc Leu	agc Ser	tta Leu	acc Thr 110	tca Ser	caa G1n	336
														gag Glu		384
ìЈу	gac Asp 130	acg Thr	atc Ile	cga Arg	gtc Val	aga Arg 135	ggc Gly	agt Ser	atc Ile	cgc Arg	aca Thr 140	tac Tyr	aga Arg	gaa G1u	gag Glu	432

cga Arg 145	Glu	att Ile	cat His	gcc Ala	acc Thr 150	Ala	tac Tyr	tat Tyr	Lys	gtg Val 155	Asp	gac Asp	cca Pro	gtg Val	tgg Trp 160	480
aac Asn	att Ile	caa Gln	att Ile	gca Ala 165	Arg	atg Met	ctt Leu	gag Glu	ctg Leu 170	Pro	act Thr	atc Ile	tac Tyr	agg Arg 175	•	528
gtt Val	tat Tyr	gac Asp	cag Gln 180	Pro	ttt Phe	cac His	agc Ser	tca Ser 185	Ala	cta Leu	gag Glu	aaa Lys	gaa Glu 190	Glu	gca Ala	576
												acg Thr 205				624
agt Ser	gaa Glu 210	aaa Lys	gcc Ala	aaa Lys	gaa Glu	ttc Phe 215	ctc Leu	atg Met	gag Glu	aac Asn	aga Arg 220	gtg Val	cag G1n	agc Ser	ttt Phe	672
tac Tyr 225	cag G1n	cag G1n	gag Glu	ctg Leu	gaa G1u 230	atg Met	gtg Val	gag Glu	tct Ser	ttg Leu 235	ctg Leu	tcc Ser	ctt Leu	gcc Ala	aat Asn 240	720
cag G1n	cct Pro	gtg Val	att Ile	cac His 245	agt Ser	gcc Ala	tgc Cys	tcc Ser	gac Asp 250	caa Gln	gtg Val	aat Asn	ttt Phe	aag Lys 255	aag Lys	768
												aat Asn				816
ctg Leu	Leu	cag G1n 275	gaa Glu	aaa Lys	gga Gly	ctt Leu	gtt Val 280	ttc Phe	cag G1n	aaa Lys	gat Asp	gat Asp 285	ggt Gly	ttt Phe	gat Asp	864
Asn	cta Leu 290	tac Tyr	tat Tyr	gta Val	Thr	aga Arg 295	gaa G1u	gac Asp	aaa Lys	Asp	ctg Leu 300	cac His	aga Arg	aag Lys	atc Ile	912
cac His 305	cgg Arg	atc Ile	att Ile	Gln	cag G1n 310	gac Asp	tgc Cys	cag G1n	Lys	cca Pro 315	aat Asn	cac His	atg Met	Glu	aag Lys 320	960

ggc t Gly (10	800
ccg g Pro G		Leu								1(056
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<211> 368

<212> PRT

<213> Homo sapiens

<400> 294

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	_			165					170					175		
Val	Tyr	Asp	Gln 180) Phe	His	Ser	Ser 185		i Leu	ı Glu	Lys	Glu 190		ı Ala	
Leu	Ser	Asn 195		Gly	' Ala	Leu	Asp 200		Pro	Ser	Leu	Thr 205		Leu	Leu	
Ser	Glu 210	Lys	Ala	Lys	Glu	Phe 215		Met	Glu	Asn	Arg 220	Val		Ser	Phe	
Tyr 225	Gln	Gln	Glu	Leu	G1u 230	Met		Glu	Ser	Leu 235	Leu		Leu	Ala	Asn 240	
		۷a٦	Ile	His 245	Ser		Cys	Ser	Asp 250	Gln	Val	Asn	Phe	Lys 255	Lys	
Asp	Thr	Thr	Ser 260	Lys		Ile	His	Ser 265	Ile		Lys	Asn	Ala 270	Ile		
Leu	Leu	G1n 275	Glu	Lys	Gly	Leu	Val 280	Phe		Lys	Asp	Asp 285			Asp	
Asn	Leu 290	Tyr	Tyr	Val	Thr	Arg 295	Glu	Asp	Lys	Asp	Leu 300		Arg	Lys	Ile	
His 305	Arg	Ile	Пe	Gln	G1n 310	Asp	Cys	Gln	Lys	Pro 315	Asn	His	Met	Glu	Lys 320	
Gly	Cys	His	Phe	Leu 325	His	Ile	Leu	Ala	Cys 330	Ala	Arg	Leu	Ser	Ile 335		
Pro	Gly	Leu	Ser 340	Glu	Ala	Val	Leu	G1n 345	Gln	Val	Leu	Glu	Leu 350		Glu	
Asp	Gln	Ser 355	Asp	Ile	Val	Ser	Thr 360	Met	Glu	His	Tyr	Tyr 365	Thr	Ala	Phe	
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	<2	20> 21> 22>	CDS (1).	(5	558)											
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tgc Cys	atc Ile	atg Met	gtc Val	ttg Leu	gtc Val	ctg Leu	gcg Ala	gtg Val	tat Tyr	gcc Ala	tac Tyr	cgc Arg	cac His	cag Gln	att Ile	96
			20					25	-		-	~	30		-	

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tca Ser	gtg Val 50	Arg	atg Met	tcc Ser	aac Asn	ctg Leu 55	gag Glu	aat Asn	gac Asp	aga Arg	gat Asp 60	gaa Glu	agg Arg	gac Asp	gac Asp	192
gac Asp 65	agc Ser	cac His	gaa Glu	gac Asp	aga Arg 70	ggc Gly	atc Ile	atc Ile	agc Ser	aac Asn 75	act Thr	cgg Arg	ttt Phe	ata Ile	gct Ala 80	240
gcg Ala	gtc Val	atc Ile	gaa Glu	cga Arg 85	cat His	gca Ala	cac His	agt Ser	cca Pro 90	gaa Glu	aga Arg	agg Arg	cgc Arg	cgc Arg 95	tac Tyr	288
tgg Trp	ggt Gly	cga Arg	tca Ser 100	gga Gly	aca Thr	gaa Glu	agt Ser	gat Asp 105	cat His	ggt Gly	tac Tyr	agc Ser	acc Thr 110	atg Met	agc Ser	336
cca Pro	cag Gln	gag Glu 115	gac Asp	agt Ser	gaa Glu	aat Asn	cct Pro 120	cca Pro	tgc Cys	aac Asn	aat Asn	gac Asp 125	ccc Pro	ttg Leu	tca Ser	384
gcc Ala	999 Gly 130	gtc Val	gat Asp	gtg Val	gga Gly	aac Asn 135	cat His	gat Asp	gag G1u	gac Asp	tta Leu 140	gac Asp	ctg Leu	gat Asp	acc Thr	432
ccc Pro 145	cct Pro	cag G1n	act Thr	gct Ala	gcc Ala 150	cta Leu	cta Leu	agt Ser	cac His	aag Lys 155	ttc Phe	cac His	cac His	tac Tyr	cgg Arg 160	480
tca Ser	cac His	cac His	cct Pro	aca Thr 165	ctt Leu	cat His	cat His	Ser	cac His 170	cac His	tta Leu	cag G1n	gcg Ala	gcc Ala 175	gtc Val	528
		His				gca Ala	Glu		taa *							558

<210> 296

<211> 185

<212> PRT

<213> Homo sapiens

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			20					25					30			
			Leu			cta Leu										14
						gac Asp 55										19
cga Arg 65	tat Tyr	caa Gln	gat Asp	cac His	ctg Leu 70	cat His	cag G1n	tgt Cys	gca Ala	gag Glu 75	gcc Ala	gtt Val	gct Ala	ttt Phe	gac Asp 80	24
						cga Arg										28
						cag Gln										33
						gtg Val										384
						cag Gln 135										432
						gag Glu										480
-			ctc Leu		ctg Leu	tag *		,								501

<210> 298

<211> 166

<212> PRT

<213> Homo sapiens

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Gln	Pro	Leu 35	Leu	Lys	Gly	Leu	Leu 40	Ser	Gly	Gln	Thr	Ser 45	Pro	Thr	Asn	
	50		Glu			55					60			•		
65			Asp		70					75					80	
			Leu	85					90					95		
			Ser 100					105					110		-	
		115	Ile				120					125			_	
	130	•	Gly			135					140					
145			Pro		150	Glu	Arg	Leu	Glu	Pro 155	Phe	Ser	Met	Lys	Pro 160	
Asp	Arg	Glu	Leu	Arg 165	Leu											
		210>														
		211>														
			DNA Homo	sap	oiens	5										
		20>	CDC													
		221> 222>	(1).	(8	328)											
			misc			;										
			(1). n =			G										
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cta Leu	gca Ala	gca Ala	gat Asp	ccg Pro	tta Leu	aac Asn	aga Arg	aga Arg	gcc Ala	atc Ile	gtc Val	cag Gln	gat Asp	cag Gln	gga Gly	96

	- 20				25				30				
	Gly		tta Leu		-	-					_		144
			gct Ala 55										192
			gga Gly									,	240
-			aca Thr				-			-	-	į	288
			ctt Leu									;	336
			tca Ser	_	_			_			•	(384
			gcc Ala 135									4	432
			aga Arg									4	480
			ttt Phe								-	ξ	528
			gat Asp									ξ	576
			atg Met									6	524

		195					200					205				
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											gag Glu					720
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	tat Tyr		tga *		,											828
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Leu	Ala	Ala	Asp 20	Pro	Leu	Asn	Arg			He	Val	Gln	Asp 30		Gly	
Cys		Pro 35		Leu	Пе		Phe 40		Asp	His	Pro	Asn 45		Pro	Val	
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Asn Val Ile Gln Lys Thr Thr Thr Pro Gly Glu Thr Lys Leu Leu Ala
Ser Glu Ile Tyr Asp Ile Leu Gln Ser Ser Asn Met Ala Asp Gly Asp
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Ser Phe Asn Glu Met Asn Ser Arg Arg Arg Lys Ala Xaa Phe Phe Leu
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Gly Thr Thr Asn Lys Arg Ala Lys Thr Val Val Leu His Ile Asp Gly
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Leu Asp Asp Thr Ser Arg Arg Asn Leu Cys Glu Glu Ala Leu Leu Lys
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                                        155
Ile Lys Gly Val Ile Ser Phe Thr Phe Gln Met Ala Val Gln Arg Cys
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                                    170
Val Val Arg Ile Arg Ser Asp Leu Lys Ala Glu Ala Leu Ala Ser Ala
                                185
Ile Ala Ser Thr Lys Val Met Lys Ala Gln Gln Val Val Lys Ser Glu
                            200
Ser Gly Glu Glu Met Leu Val Pro Phe Gln Asp Thr Pro Val Glu Val
                        215
                                            220
Glu Gln Asn Thr Glu Leu Pro Asp Tyr Leu Pro Glu Asp Glu Ser Pro
                    230
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Thr Lys Glu Gln Asp Lys Ala Val Ser Arg Val Gly Ser His Pro Glu
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Phe Tyr Trp
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					act Thr											144
					aaa Lys 55											192
					aat Asn											240
					cat His								-			288
-				-	cag Gln	_	-		_	_	-				•	336
 	-		-	-	gag Glu	-	-			-	-		-	~		384
	-	-			tta Leu 135		_			-		-				432
					gct Ala	-					_			_		480
					aga Arg											528
					gat Asp			-	-	_			_			576

				G1n		tca Ser				624
			-			att Ile 220	Leu	_	•	672
						aca Thr				720
						gat Asp				768
						gaa Glu				816
						aag Lys				864
						ggt Gly 300				912
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Lys Gly Lys Gly Arg Asn Thr Gly Lys Ser Gln Thr Leu Gly Ser Lys
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Ser Thr Thr Asn Glu Lys Lys Arg Glu Lys Arg Arg Lys Lys Glu
                        55
Gln Gln Gln Ser Glu Ala Asn Glu Leu Arg Asn Leu Ala Phe Lys Lys
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                                        75
Ile Pro Gln Lys Ser Ser His Ala Val Cys Asn Ala Gln His Asp Leu
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Pro Leu Ser Asn Pro Val Gln Lys Asp Ser Arg Glu Glu Asn Trp Gln
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Glu Trp Arg Gln Arg Asp Glu Gln Leu Thr Ser Glu Met Phe Glu Ala
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                                                125
Asp Leu Glu Lys Ala Leu Leu Leu Ser Lys Leu Glu Tyr Glu Glu His
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Lys Lys Glu Tyr Glu Asp Ala Glu Asn Thr Ser Thr Gln Ser Lys Val
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                                        155
Met Asn Xaa Lys Asp Lys Arg Lys Asn His Gln Gly Lys Asp Arg Pro
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                                    170
Leu Thr Val Ser Leu Lys Asp Phe His Ser Glu Asp His Ile Ser Lys
                                185
Lys Thr Glu Glu Leu Ser Ser Ser Gln Thr Leu Ser His Asp Gly Gly
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Phe Phe Asn Arg Leu Glu Asp Asp Val His Lys Ile Leu Ile Arg Glu
Lys Arg Arg Glu Gln Leu Thr Glu Tyr Asn Gly Thr Asp Asn Cys Thr
                                        235
Ala His Glu His Asn Gln Glu Val Val Leu Lys Asp Gly Arg Ile Glu
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Lys	Asn	Va1 275		Thr	Glr	Trp	G1u 280	Ala		Tyr	Lys	G1u 285	۷a٦		Ala	
	290					295					300			_	Asp	
305	,				310					315					Asn 320	
				325					330					335		
Arg	Ser	Lys	Va1 340	Lys	Val	Leu	Gln	A1a 345		Leu	Ala	Lys	Tyr 350		Gly	
Gly	Arg	Lys 355		Lys	Arg	Asn	Ser 3 <u>.</u> 60		Ser	Asp	Gln	Cys 365	Arg			
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	acc Thr															9
aac Asn	ttg Leu	gag G1u 35	aaa Lys	aca Thr	att Ile	ttc Phe	tgc Cys 40	ctg Leu	cag Gln	aaa Lys	ctg Leu	att Ile 45	tct Ser	ttg Leu	cat His	144
cct Pro	ttt Phe 50	aat Asn	cct Pro	tgg Trp	aac Asn	tgg Trp 55	ggc Gly	aaa Lys	ttg Leu	gca Ala	gag G1u 60	gct Ala	tac Tyr	ctg Leu	aat Asn	192
ctg Leu	999 Gly	cca Pro	gct Ala	ctt Leu	tca Ser	gca Ala	gca Ala	ctt Leu	gcg Ala	tca Ser	tct Ser	cag G1n	aaa Lys	cag Gln	cac His	240

65					70					75					80	
-				-	_										tca Ser	288
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								agt Ser								384
								atg Met			-	-	-			432
								tgt Cys							agg Arg 160	480
								cag Gln			_		-	-		528
							-	att Ile 185				-				576
								ttg Leu								624
								gaa Glu								672
				Ala				ttg Leu								720
ttt Phe	gaa Glu	gac Asp	aag Lys	tgg Trp	ttc Phe	aga Arg	aag Lys	atc Ile	aaa Lys	gac Asp	cat His	ttc Phe	tgt Cys	cca Pro	ttt Phe	768

WO 01/29221

448

245 250 255

gaa aat cag ttc cat aca gag ata caa atc ttg gct tag Glu Asn Gln Phe His Thr Glu Ile Gln Ile Leu Ala * 260 265

807

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Leu Gly Pro Ala Leu Ser Ala Ala Leu Ala Ser Ser Gln Lys Gln His 65 70 75 80

Ser Phe Thr Ser Ser Asp Lys Thr Ile Lys Ser Phe Phe Pro His Ser 85 90 95

Gly Lys Asp Cys Leu Leu Cys Phe Pro Glu Thr Leu Pro Glu Ser Ser 100 105 110

Leu Phe Ser Val Glu Ala Asn Ser Ser Asn Ser Gln Lys Asn Glu Lys 115 120 125

Ala Leu Thr Asn Ile Gln Asn Cys Met Ala Glu Lys Arg Glu Thr Val 130 135 140

Leu Ile Glu Thr Gln Leu Lys Ala Cys Ala Ser Phe Ile Arg Thr Arg 145 150 155 160

145 150 155 160 Leu Leu Gln Phe Thr Gln Pro Gln Gln Thr Ser Phe Ala Leu Glu

165 170 175

Arg Asn Leu Arg Thr Gln Gln Glu Ile Glu Asp Lys Met Lys Gly Phe
180 185 190

180 185 190
Ser Phe Lys Glu Asp Thr Leu Leu Leu Ile Ala Glu Val Met Gly Glu
195 200 205

Asp Ile Pro Glu Lys Ile Lys Asp Glu Val His Pro Glu Val Lys Cys 210 215 220

Val Gly Ser Val Ala Leu Thr Ala Leu Val Thr Val Ser Ser Glu Glu 225 230 235 240

Phe Glu Asp Lys Trp Phe Arg Lys Ile Lys Asp His Phe Cys Pro Phe

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						ggg Gly										144
						atg Met 55										192
						gcc Ala										240
acc Thr	atc Ile	caa Gln	gtg Val	gcc Ala 85	att Ile	cag Gln	agt Ser	tta Leu	cgt Arg 90	ttc Phe	ttc Phe	aac Asn	agc Ser	ttt Phe 95	gca Ala	288
						ttt Phe										336
tcc Ser	ctt Leu	gca Ala	ttc Phe	cgg Arg	cac His	atg Met	gcc Ala	agc Ser	tcc Ser	ctg Leu	ctg Leu	ggc Gly	cac His	tgc Cys	agc Ser	384

	115			120				125			
							atc Ile 140				432
							atc Ile				480
							ttg Leu				528
			-		-	-	cct Pro			_	576
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			aat Asn													192
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			tgg Trp													288
			aag Lys 100													336
			tcc Ser								_	_				384
			act Thr													432
			aac Asn													480
cta Leu	cct Pro	cgg Arg	ttc Phe	tac Tyr	cag Gln	gct Ala	tct Ser	att Ile	gtg Val	gct Ala	gag Glu	gcc Ala	tac Tyr	gat Asp	ttt Phe	528

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				Ala					Gln					Lys	gga Gly	576
			Tyr					Lys					Leu		tcc Ser	624
		Phe										His			act Thr	672
	Met										Thr				gat Asp 240	720
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		gca Ala 275		tag *	,		*									831
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1 Thr	Asp	Thr	Leu 20	5 Leu	Phe	Pro	Phe	Tyr 25	10 Ser	Gly	Pro	Ser	_	15 Thr	Leu	
Lys	Thr	A1a 35		Leu	Asp	Tyr	Ile 40		Arg	Cys	Arg	Pro 45	30 Gly	Asp	Ser	
Glu	Lys	His	Asn	Met	Ile	Ala	Leu	Cys	Phe	Ser	Met	Cys	Arg '	Glu	Ile	

WO 01/29221 PCT/US00/29052

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Gly 65	Glu	Asn	His	Glu	A1a 70	Ala	Ala	Arg	Ile	G1n 75	Leu	Lys	Leu	Пe	G1u 80	
	Gln	Pro	Trp	G1u 85		Ser	Leu	Lys	Asp 90	-	His	Gln	Leu	Lys 95		
Leu	Leu	Leu	Lys 100	Ala	Leu	Thr	Leu	Met 105	Leu	Asp	Ala	Ala	Glu 110	Ser	Tyr	
	Lys	115					120				_	125	_			
	Leu 130					135					140					
145	Leu				150					155	•				160	
	Pro			165					170				-	175		
	Pro		180					185					190			
•	Phe	195					200				_	205		•		
	11e 210					215					220					
225	Met				230		-			235		-	-		240	
	Tyr			245					250					255		
	Asn		260	Leu	Lys	Asp	Pro	G1n 265	Thr	Gly	Cys	Cys	Leu 270	Lys	Asp	
Met	Leu	A1 a 275	G1y													
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									1 7 7							
									gat Asp						aaa Lys	96
					_	_	-	-	cat His	_	_	-	-	_	•	144
									gca Ala						_	192
									tta Leu							240
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									aag Lys							336
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Gln	Leu	Tyr 35		Ser	Leu	Met	Ala 40		His	Ala	Ser	Arg 45		Arg	Val	
	Lys 50		Cys	Пе	Ala	G1n 55		Ser	Ala	Val	Val 60		Asn	Leu	Arg	
		Arg	Glu	Lys	Asn		Asp	Asp	Leu	Thr		Leu	Lys	G1n	Leu	

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Arg	Lys	Glu	Gln	Thr 85	Lys	Leu	Lys	Trp	Met 90	Gln	Ser	Glu	Leu	Asn 95	Val	
			100			Arg		105		۷a٦	Phe	Asn	Glu 110	Arg	Cys	
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						atg Met										240
						gcc Ala										288
						gag										336

			100					105					110			
											cca Pro					384
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											gga Gly				_	480
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	cac His	_		_		tga *										549
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Met	Gln	Arg 35		Ser	Leu	Arg	Phe 40		Gly	Pro	Met	Thr 45		Ser	Tyr	
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GTu 65		Glu	Asn	Asp	Ala 70		Ala	Asp	Ala	Asp 75	Arg	Leu	Ala	Gly	Pro 80	
	Ala	A1a ⁻	Glu	Leu 85		Ala	Ala	Thr	Va1 90		Thr	Gly	Phe	Ser 95		
Ser	Ser	Ala	Ile 100		Glu	Glu	Asp	Gly 105		Ser	Glu	Glu	Gly 110		Val	
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Pro 145	Ser	Ser	Trp	Gly	Ala 150		Pro	Ala	Pro	His 155	Gly	Ala	Gln	Ala	Leu 160	
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	ctt Leu															96
ctc Leu	ttc Phe	aac Asn 35	agt Ser	gtg Val	gcc Ala	ttt Phe	caa G1n 40	aat Asn	gca Ala	gat Asp	gcc Ala	acc Thr 45	agg Arg	aga Arg	aca Thr	144
	cca Pro 50															192
	cag Gln									tga *						225

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                                     10
ccg ctg tgg tcc tcc tca ctg cct ggg ctg gac act gct gaa agt aaa
                                                                       96
Pro Leu Trp Ser Ser Ser Leu Pro Gly Leu Asp Thr Ala Glu Ser Lys
             20
gcc acc att gca gac ctg atc ctg tct gcg ctg gag aga gcc acc gtc
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Ala Thr Ile Ala Asp Leu Ile Leu Ser Ala Leu Glu Arg Ala Thr Val
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												gag Glu				240
												999 Gly				288
												tac Tyr				336
												ctc Leu 125				384
												gcc Ala				432
												gag Glu				480
												agc Ser				528
							Arg					aag Lys				576
	Gly											ctc Leu 205				624
Met					Gln					G7n		cag Gln				672

	Leu		tgc Cys													720
			gcc Ala													768
			atg Met 260													816
			ctc Leu													864
			gaa Glu													912
			agg Arg													960
tgc Cys	tcc Ser	tcc Ser	cac His	aac Asn 325	aca Thr	gcc Ala	aca Thr	gca Ala	gtg Val 330	gca Ala	gcc Ala	ctg Leu	ggt Gly	ggc Gly 335	ttc Phe	1008
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Ala	Thr	Ile 35	Ala	Asp	Leu	Ile	Leu 40	Ser	Ala	Leu	Glu	Arg 45		Thr	۷a٦
Phe	Leu 50	Glu	Gln	Arg	Leu	Pro 55	Glu	Ile	Asn	Leu	Asp 60		Met	Val	Gly
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				85		,			90					95	Gly
			100					105					110	Ť	Leu
		115				Arg	120					125			ŭ
	130					Ala 135					140				
145					150	Gln				155			_		160
				165		Leu			170					175	
			180			Cys		185					190	_	_
		195				His	200					205			
	210					Gly 215					220				
225					230	Met				235					240
				245		Thr			250					255	
			260			Phe		265					270	,	
		275				G1n	280					285		_	
	290					G1u 295					300				
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				325		Ala			330				•	335	
Leu	Tyr		Leu 340	Ala	Glu	Tyr		Pro 345	Ala	Asn	Arg	G1u	Pro 350	His	Pro

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														ctg Leu		96
														gag Glu		144
														cgg Arg		192
	Asn					Glu		Pro	Leu	Ser	Val	Pro	Arg	gat Asp	Āla	240
ccg Pro	ttc Phe	cag Gln	ctg Leu	gag Glu 85	acc Thr	tgc Cys	ccc Pro	ctc Leu	acg Thr 90	acc Thr	gtg Val	gat Asp	gcc Ala	ctg Leu 95	gtc Val	288
														gtg Val		336

				ctc Leu									384
				aac Asn									432
				atg Met 150					 -			_	480
				 gag Glu	_	_	_			~			528
				atg Met									 576
				cct Pro									624
				cag Gln									672
				gga Gly 230						-		-	720
				ggc Gly				_			-	-	768
-		Met	_	 gac Asp	_	_	_	_		_			816
	Phe			ctg Leu	Phe								864

		Asp										acg Thr				912
ctg Leu 305	Leu	tcc Ser	gat Asp	tct Ser	gcc Ala 310	ttc Phe	gac Asp	tct Ser	999 Gly	cgc Arg 315	ctc Leu	tgg Trp	ttg Leu	ctg Leu	gtg Val 320	960
												cac His				1008
									_		_	cga Arg			-	1056
												gtc Val 365				1104
												ccg Pro				1152
												ggc Gly				1200
												tcc Ser				1248
												cag Gln				1296
	Ile					Gly						ctc Leu 445				1344
Gly	gtc Val 450	ctg Leu	gcc Ala	tac Tyr	Leu	atc Ile 455	tgg Trp	tgg Trp	acg Thr	Ala	gcc Ala 460	tgc Cys	cag G1n	ctg Leu	ctc Leu	1392

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Pro Leu Lys Lys Gln Gly Trp Asp Trp Ala Leu Pro Val Ala Lys

210 215 . 220 Leu Ala Ile Arg Val Gly Leu Ala Val Val Gly Ser Val Leu Gly Ala 230 235 Phe Leu Thr Phe Pro Gly Leu Arg Leu Ala Gln Thr His Arg Asp Ala 250 Leu Thr Met Ser Glu Asp Arg Pro Met Leu Gln Phe Leu Leu His Thr 260 265 Ser Phe Leu Ser Pro Leu Phe Ile Leu Trp Leu Trp Thr Lys Pro Ile 280 Ala Arg Asp Phe Leu His Gln Pro Pro Phe Gly Glu Thr Arg Phe Ser 295 Leu Leu Ser Asp Ser Ala Phe Asp Ser Gly Arg Leu Trp Leu Leu Val 310 315 Val Leu Cys Leu Leu Arg Leu Ala Val Thr Arg Pro His Leu Gln Ala 330 Tyr Leu Cys Leu Ala Lys Ala Arg Val Glu Gln Leu Arg Arg Glu Ala 345 Gly Arg Ile Glu Ala Arg Glu Ile Gln Gln Arg Val Val Arg Val Tyr 360 Cys Tyr Val Thr Val Val Ser Leu Gln Tyr Leu Thr Pro Leu Ile Leu 375 380 Thr Leu Asn Cys Thr Leu Leu Leu Lys Thr Leu Gly Gly Tyr Ser Trp 390 395 Gly Leu Gly Pro Ala Pro Leu Leu Ser Pro Asp Pro Ser Ser Ala Ser 410 Ala Ala Pro Ile Gly Ser Gly Glu Asp Glu Val Xaa Gln Thr Ala Ala 425 Arg Ile Ala Gly Ala Leu Gly Gly Leu Leu Thr Pro Leu Phe Leu Arg 440 Gly Val Leu Ala Tyr Leu Ile Trp Trp Thr Ala Ala Cys Gln Leu Leu 455 Ala Ser Leu Phe Gly Leu Tyr Phe His Gln His Leu Ala Gly Ser 465

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	tct Ser	gtc Val	act Thr	gga Gly 20	tct Ser	ggt Gly	ttc Phe	agt Ser	gtc Val 25	Ser	gad Asp	ctt Leu	gco IAla	cca Pro 30	Pro	cgg Arg	Š	96
														Leu		gat Asp	14	14
	ggc Gly	tct Ser 50	gag Glu	aga Arg	ttc Phe	ctc Leu	tgc Cys 55	gaa G1u	tct Ser	gtt Val	ttt Phe	agc Ser 60	Tyr	caa Gln	gtg Val	gca Ala	19)2
	tcc Ser 65	acg Thr	ctt Leu	aaa Lys	cag Gln	gtg Val 70	aaa Lys	cat His	gat Asp	cag G1n	caa Gln 75	Val	gct Ala	cgg Arg	atg Met	gaa Glu 80	24	.0
	aaa Lys	cta Leu	gct Ala	ggt Gly	ttg Leu 85	gta Val	gaa Glu	gag G1u	ctg Leu	gag G1u 90	gct Ala	gac Asp	gag G1u	tgg Trp	cgg Arg 95	ttt Phe	28	8
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	Lys /	Ala l			Thr	Tyr				Ala	Gly	Glu	Met 45	Leu	Glu	Asp		
	Gly S			Arg	Phe				Ser	Val	Phe	Ser 60	Tyr	Gln	Val	Ala		
	<u>-</u>	TI 1							_				_					

Ser Thr Leu Lys Gln Val Lys His Asp Gln Gln Val Ala Arg Met Glu

65 Lys	Leu	ı Alā	ı Gly	/ Leu 85	70 Val	Glu	ı Glu	ı Lei	ս G1 ս 90	75 1 Alā	a Asp	Glu	ı Trp	95	80 Phe	
Lys	Pro	l]∈	9 Glu 100	ı Gln	Leu	. Leu	G1y	Phe 105		Pro	Ser	· Ser	Gly 110	,		
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gaa Glu	999 Gly	gat Asp	gta Val 20	atg Met	cag G1n	ctg Leu	aaa Lys	tca Ser 25	gaa Glu	gcc Ala	atc Ile	cag Gln	acc Thr 30	tct Ser	cat His	96
ttt Phe	caa G1n	ggc Gly 35	aga Arg	ctt Leu	aat Asn	gaa Glu	gtc Val 40	att Ile	aga Arg	acc Thr	tta Leu	act Thr 45	cag G1n	gtc Val	att Ile	144
agt Ser	gtc Val 50	tct Ser	ggg Gly	gtg Val	att Ile	ggt Gly 55	ctc Leu	cag Gln	tca Ser	aat Asn	gca Ala 60	gtc Val	tgg Trp	ctt Leu	ctt Leu	192
gga Gly 65	cat His	ctt Leu	cat His	cta Leu	tct Ser 70	act Thr	cta Leu	tcc Ser	tca Ser	agt Ser 75	caa Gln	agt Ser	aga Arg	gcc Ala	tct Ser 80	240
tt al	cct Pro	act Thr	gac Asp	tat Tyr 85	agc Ser	tac Tyr	ttg Leu	cct Pro	gaa Glu 90	agc Ser	agt Ser	ttt Phe	att Ile	gga Gly 95	gca Ala	288

gct Ala	att Ile	ggc Gly	tto Phe	Phe	att Ile	aca Thr	gga Gly	1 gga 105	' Lys	l aaa Lys	ggt Gly	cct Pro	gaa Glu 110	ı Ser	gtg Val	336
cct Pro	cct Pro	tco Ser 115	Leu	ctt Leu	aaa Lys	gta Val	gtg Val 120	Met	aaa Lys	ccc Pro	ata Ile	gca Ala 125	Thr	gtt Val	gga Gly	384
gaa Glu	agc Ser 130	Tyr	caa Gln	tat Tyr	cct Pro	cct Pro 135	۷a٦	aac Asn	tgg Trp	gct Ala	gca Ala 140	Leu	ctc Leu	tct Ser	cca Pro	432
ctt Leu 145	atg Met	agg Arg	cta Leu	aat Asn	ttt Phe 150	ggt Gly	gaa Glu	gag Glu	atc Ile	cag Gln 155	G1n	ctg Leu	tgc Cys	ctt Leu	gaa Glu 160	480
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ggc Gly	ttg Leu	tgg Trp	gtg Val 180	aca Thr	cca Pro	cca Pro	ctg Leu	atc Ile 185	cac His	agt Ser	ctg Leu	agt Ser	ctg Leu 190	aat Asn	acc Thr	576
aag Lys	aga Arg	tat Tyr 195	ctc Leu	ctg Leu	ata Ile	tct Ser	gca Ala 200	cct Pro	ctg Leu	tgg Trp	ata Ile	aaa Lys 205	cac His	atc Ile	tct Ser	624
gat Asp	gaa Glu 210	cag Gln	atc Ile	ctg Leu	ggt Gly	ttt Phe 215	gtt Val	gaa Glu	aat Asn	tta Leu	atg Met 220	gtg Val	gca Ala	gtt Val	ttt Phe	672
aaa Lys 225	gca Ala	gct Ala	tcc Ser	cca Pro	ctt Leu 230	gga Gly	agt Ser	cct Pro	gag Glu	cta Leu 235	tgc Cys	cca Pro	agt Ser	gct Ala	tta Leu 240	720
						atg Met										768
tgg Γrp	agt Ser	ctg Leu	ctc Leu 260	tct Ser	gaa Glu	gct Ala	Thr	999 Gly 265	aaa Lys	att Ile	ttt Phe	Asp	ctc Leu 270	ctg Leu	cca Pro	816

aat Asn	aag Lys	att : Ile : 275	e Arg	g aga g Arg	a aag J Lys	g gat S Asp	cta Leu 280	ı Glu	g ctq u Leu	j tai ı Tyr	ato	c ago e Ser 285	116	a goa e Ala	a aaa a Lys	864
tgc Cys	cto Leu 290	Leu	gaa Glu	a atg u Met	aca Thr	gat Asp 295	Asp	gat Asp	gcc Ala	aat Asr	cg Arg 300	j Ile	gco Ala	caç Glr	ggtt val	912
act Thr 305	Lys	agc Ser	aac Asr	ata Ile	gaa Glu 310	Lys	gct Ala	gcc	ttt Phe	gtc Val 315	Lys	a ctg Leu	tac Tyr	: tta : Leu	gtc Val 320	960
tct Ser	caa Gln	gga Gly	cga Arg	ttc Phe 325	Pro	ttg Leu	gtg Val	aac Asn	ctg Leu 330	Thr	gat Asp	atg Met	ctg Leu	aga Arg 335	ttt Phe	1008
gca Ala	acc Thr	gca Ala	gtg Val 340		gca Ala	tgg Trp	gct Ala	gac Asp 345	His	act Thr	gcc Ala	cct Pro	ctc Leu 350	Leu	ctc Leu	1056
ggc Gly	ctc Leu	agt Ser 355	gcc Ala	agt Ser	tgg Trp	ttg Leu	cca Pro 360	tgg Trp	cat His	cag G1n	gag Glu	aat Asn 365	ggc Gly	ccg Pro	gct Ala	1104
999 Gly	cca Pro 370	gta Val	cca Pro	agc Ser	ttc Phe	ctt Leu 375	ggc Gly	agg Arg	agt Ser	cca Pro	atg Met 380	cac His	agg Arg	gtc Val	act Thr	1152
ctg Leu 385	cag G1n	gag Glu	gtt Val	ctc Leu	act Thr 390	ctc Leu	ctt Leu	ccc Pro	aat Asn	agc Ser 395	atg Met	gct Ala	ctg Leu	ctg Leu	ctg Leu 400	1200
cag Gln	aaa Lys	gag Glu	cca Pro	tgg Trp 405	aag Lys	gaa Glu	cag Gln	acc Thr	cag Gln 410	aag Lys	ttc Phe	att Ile	gac Asp	tgg Trp 415	cta Leu	1248
ttc Phe	agc Ser	He	atg Met 420	gaa G1u	agc Ser	cct Pro	Lys	gaa Glu 425	gcc Ala	ctc Leu	tca Ser	gca Ala	cag Gln 430	tcc Ser	agg Arg	1296
gat Asp	Leu	ttg Leu 435	aaa Lys	gcc Ala	acc Thr	Leu	ctg Leu 440	tcc Ser	ttg Leu	aga Arg	gtt Val	ctc Leu 445	cca Pro	gag Glu	ttt Phe	1344

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Phe Gln Gly Arg Leu Asn Glu Val Ile Arg Thr Leu Thr Gln Val Ile
                            40
Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
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Gly His Leu His Leu Ser Thr Leu Ser Ser Gln Ser Arg Ala Ser
Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
                                105
Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
                            120
Glu Ser Tyr Gln Tyr Pro Pro Val Asn Trp Ala Ala Leu Leu Ser Pro
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                                            140
Leu Met Arg Leu Asn Phe Gly Glu Glu Ile Gln Gln Leu Cys Leu Glu
                    150
                                        155
Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Ala Leu Leu
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Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
                                185
                                                    190
Lys Arg Tyr Leu Leu Ile Ser Ala Pro Leu Trp Ile Lys His Ile Ser
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Asp Glu Gln Ile Leu Gly Phe Val Glu Asn Leu Met Val Ala Val Phe
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Lys 225	Ala	Ala	Ser	Pro	Leu 230	Gly	Ser	Pro	Glu	Leu 235		Pro	Ser	Ala	Leu 240
His	Gly	Leu	Ser	G1n 245	Ala	Met	Lys	Leu	Pro 250	Ser		Ala	His	His 255	Leu
Trp	Ser	Leu	Leu 260	Ser	Glu	Ala	Thr	Gly 265		Ile	Phe	Asp	Leu 270	Leu	Pro
		275	Arg				280					285			
	290		Glu			295					300				
305			Asn		310					315					320
			Arg	325					330					335	
			Va1 340					345					350		
		355	Ala				360					365	•		
	370		Pro			375					380				
385			Val		390					395					400
			Pro	405					410					415	
			Met 420					425					430		_
		435	Lys				440						Pro	Glu	Phe
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gaa Glu	999 Gly	gat Asp	gta Val 20	Met	cag Gln	ctg Leu	aaa Lys	tca Ser 25	· Glu	gcc Ala	ato Ile	cag e Gln	acc Thr	Ser	cat His	96	
			Arg					He					Gln		att Ile	144	
agt Ser	gtc Val 50	. Ser	999 Gly	gtg Val	att Ile	ggt Gly 55	Leu	cag Gln	tca Ser	aat Asn	gca Ala 60	Val	tgg Trp	ctt Leu	ctt Leu	192	
gga Gly 65	cat His	ctt Leu	cat His	cta Leu	tct Ser 70	act Thr	cta Leu	tcc Ser	tca Ser	agt Ser 75	Gln	agt Ser	aga Arg	gcc Ala	tct Ser 80	240	
gtt Val	cct Pro	act Thr	gac Asp	tat Tyr 85	agc Ser	tac Tyr	ttg Leu	cct Pro	gaa Glu 90	agc Ser	agt Ser	ttt Phe	att Ile	gga Gly 95	gca Ala	288	
gct Ala	att Ile	ggc Gly	ttc Phe 100	ttc Phe	att Ile	aca Thr	gga Gly	gga Gly 105	aaa Lys	aaa Lys	ggt Gly	cct Pro	gaa Glu 110	tct Ser	gtg Val	336	
cct Pro	cct Pro	tcc Ser 115	ctt Leu	ctt Leu	aaa Lys	gta Val	gtg Val 120	atg Met	aaa Lys	ccc Pro	ata Ile	gca Ala 125	act Thr	gtt Val	gga Gly	384	
Glu	agc Ser 130	tac Tyr	caa G1n	tat Tyr	cct Pro	cct Pro 135	gtg Val	aac Asn	tgg Trp	gct Ala	gca Ala 140	Leu	ctc Leu	tct Ser	cca Pro	432	
ctt Leu 145	atg Met	agg Arg	cta Leu	aat Asn	ttt Phe 150	ggt Gly	gaa Glu	gag Glu	atc Ile	cag Gln 155	caa G1n	ctg Leu	tgc Cys	ctt Leu	gaa Glu 160	480	
att Ile I	atg Met	gtg Val	acc Thr	cag Gln 165	gca Ala	cag G1n	tca Ser	Ser	cag Gln 170	aat Asn	gca Ala	gct Ala	gca Ala	cta Leu 175	ttg Leu	528	

				Thr					His					Asn	acc Thr	576
aag Lys	aga Arg	tat Tyr 195	Leu	ctg Leu	ata Ile	tct Ser	gca Ala 200	Pro	ctg Leu	tgg Trp	ata Ile	aaa Lys 205	His	atc Ile	tct Ser	624
												Val			ttt Phe	672
										cta Leu 235	Cys					720
										agc Ser						768
										att Ile						816
										tat Tyr						864
										aat Asn						912
										gtc Val 315						960
								Asn		acc Thr						1008
gct Ala	gtg Val	Gln	cac His 340	cgt Arg	gag Glu	aaa Lys	Glu	gtg Val 345	ttg Leu	gcc Ala	tgg Trp	Met	att Ile 350	ctg Leu	cac His	1056

ago Ser	tta Leu	tac Tyr 355	Gln	gca Ala	cgg Arg	att Ile	gtg Val 360	Ser	cat His	gcc Ala	aat Asn	acg Thr 365	Gly	gtt Val	ttg Leu		1104
aag Lys	aga Arg 370	Met	gag Glu	tgg Trp	ctc Leu	ttg Leu 375	gaa Glu	ctg Leu	atg Met	ggt Gly	tat Tyr 380	He	aga Arg	aat Asn	gtt Val		1152
gct Ala . 385	Tyr	cag Gln	tca Ser	aca Thr	tcc Ser 390	ttt Phe	cac His	aat Asn	acg Thr	gct Ala 395	ctt Leu	gac Asp	gag Glu	gct Ala	ttg Leu 400		1200
						ttt Phe				Val							1248
cac His	act Thr	gcc Ala	cct Pro 420	ctc Leu	ctc Leu	ctc Leu	ggc Gly	ctc Leu 425	agt Ser	gcc Ala	agt Ser	tgg Trp	ttg Leu 430	cca Pro	tgg Trp		1296
						gct Ala											1344
agt Ser	cca Pro 450	atg Met	cac His	agg Arg	gtc Val	act Thr 455	ctg Leu	cag Gln	gag Glu	gtt Val	ctc Leu 460	act Thr	ctc Leu	ctt Leu	ccc Pro		1392
aat Asn 465	agc Ser	atg Met	gct Ala	ctg Leu	ctg Leu 470	ctg Leu	cag Gln	aaa Lys	gag Glu	cca Pro 475	tgg Trp	aag Lys	gaa Glu	cag Gln	acc Thr 480	1	1440
cag Gìn	aag Lys	ttc Phe	He	gac Asp 485	tgg Trp	cta Leu	ttc Phe	agc Ser	atc Ile 490	atg Met	gaa Glu	agc Ser	cct Pro	aaa Lys 495	gaa Glu	1	1488
gcc Ala	ctc Leu	tca Ser	gca Ala 500	cag Gln	tcc Ser	agg Arg	Asp	ctt Leu 505	ttg Leu	aaa Lys	gcc Ala	acc Thr	ctg Leu 510	ctg Leu	tcc Ser	1	.536
ttg Leu	Arg	gtt Val 515	ctc Leu	cca Pro	gag Glu	ttt Phe	aag Lys 520	aag Lys	aaa Lys	gct Ala	Val	tgg Trp 525	acc Thr	aga Arg	gca Ala	. 1	.584

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Ser Val Ser Gly Val Ile Gly Leu Gln Ser Asn Ala Val Trp Leu Leu
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Gly His Leu His Leu Ser Thr Leu Ser Ser Gln Ser Arg Ala Ser
                    70
Val Pro Thr Asp Tyr Ser Tyr Leu Pro Glu Ser Ser Phe Ile Gly Ala
                                    90
Ala Ile Gly Phe Phe Ile Thr Gly Gly Lys Lys Gly Pro Glu Ser Val
                                105
Pro Pro Ser Leu Leu Lys Val Val Met Lys Pro Ile Ala Thr Val Gly
                            120
Glu Ser Tyr Gln Tyr Pro Pro Val Asn Trp Ala Ala Leu Leu Ser Pro
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Leu Met Arg Leu Asn Phe Gly Glu Glu Ile Gln Gln Leu Cys Leu Glu
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                                        155
Ile Met Val Thr Gln Ala Gln Ser Ser Gln Asn Ala Ala Leu Leu
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                                    170
Gly Leu Trp Val Thr Pro Pro Leu Ile His Ser Leu Ser Leu Asn Thr
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	Ser		260					265					270	Leu	Pro
	Lys	275					280					285			_
	Leu 290					295					300				
305					310					315					320
	Gln			325				*	330					335	
	Val		340					345					350		
	Leu	355					360					365			
	Arg 370					375					380				
385	Tyr				390					395					400
	Phe			405					410					415	·
	Thr		420					425					430		•
	Gln	435					440					445			
	Pro 450					455					460				
465	Ser				470					475					480
	Lys			485					490					495	
	Leu		500					505					510		
Leu	Arg	Va7 515	Leu	Pro	Glu		Lys 520	Lys	Lys	Ala		Trp 525	Thr	Arg	Ala
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tgg Trp	gtg Val	cga Arg	ggc Gly 20	Ser	ggc Gly	cct Pro	tcc Ser	gtg Val 25	Leu	ago Ser	cgc Arg	ctg Leu	cag Gln 30	Asp	gcg Ala	96
gcc Ala	gtg Val	gtg Val 35	cgg Arg	cct Pro	ggc Gly	ttc Phe	ctg Leu 40	Ser	acg Thr	gca Ala	gag Glu	gag Glu 45	Glu	acg Thr	ctg Leu	144
agc Ser	cga Arg 50	gaa Glu	ctg Leu	gag Glu	ccc Pro	gag Glu 55	ctg Leu	cgc Arg	cgc Arg	cgc Arg	cgc Arg 60	Tyr	gaa Glu	tac Tyr	gat Asp	192
cac His 65	tgg Trp	gac Asp	gcg Ala	gcc Ala	atc Ile 70	cac His	ggc Gly	ttc Phe	cga Arg	gag Glu 75	aca Thr	gag Glu	aag Lys	tcg Ser	cgc Arg 80	240
tgg Trp	tca Ser	gaa Glu	gcc Ala	agc Ser 85	cgg Arg	gcc Ala	atc Ile	ctg Leu	cag G1n 90	cgc Arg	gtg Val	cag Gln	gcg Ala	gcc Ala 95	gcc Ala	288
ttt Phe	ggc Gly	ccc Pro	ggc Gly 100	cag Gln	acc Thr	ctg Leu	ctc Leu	tcc Ser 105	tcc Ser	gtg Val	cac His	gtg Val	ctg Leu 110	gac Asp	ctg Leu	336
gaa Glu	Ala	cgc Arg 115	ggc Gly	tac Tyr	atc Ile	aag Lys	ccc Pro 120	cac His	gtg Val	gac Asp	agc Ser	atc Ile 125	aag Lys	ttc Phe	tgc Cys	384
aly .	gcc Ala 130 _.	acc Thr	atc Ile	gcc Ala	ggc Gly	ctg Leu 135	tct Ser	ctc Leu	ctg Leu	tct Ser	ccc Pro 140	agc Ser	gtt Val	atg Met	cgg Arg	432

L	tg eu 45	gtg Val	cac His	acc Thr	cag Gln	gag Glu 150	Pro	ggg Gly	gag Glu	tgg Trp	ctg Leu 155	Glu	cto Leu	ttg Leu	ctg Leu	gag Glu 160	480
C: Pi	cg ro	ggc Gly	tcc Ser	ctc Leu	tac Tyr 165	He	ctt Leu	agg Arg	ggc Gly	tca Ser 170	Ala	cgt Arg	tat Tyr	gac Asp	ttc Phe 175	tcc Ser	528
										Phe						att Ile	576
															gag Glu	ggc Gly	624
							gga Gly 215					-	•	tga *			666
		<2 <2			o sap	oiens	ŝ										
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		Val	Arg	Gly 20		Gly	Pro	Ser	Va1 25		Ser	Arg	Leu	G1n 30	Asp	Ala	
Αl	a	Val	Va1 35		Pro	Gly	Phe	Leu 40		Thr	Ala	Glu			Thr	Leu	
Se		Arg 50		Leu	Glu	Pro	G1u 55		Arg	Arg	Arg	Arg 60	45 Tyr	Glu	Tyr	Asp	
Hi 65	S		Asp	Ala	Ala	I1e 70		Gly	Phe	Arg	G1u 75		Glu	Lys	Ser		
		Ser	Glu				Ala	Пe	Leu			Val	Gln	Ala	Ala	80 Ala	
Ph	e i	Gly	Pro	Gly	85 G1n	Thr	Leu	Leu		90 Ser	Val	His	Val		95 Asp	Leu	
G1	u ,			100 Gly	Tyr	Ile	Lys		105 His	Val	Asp	Ser		110 Lys	Phe	Cys	
G1	V		115 Thr	Πe	Ala	G1 v	Leu	120 Ser	Leu	l eu	Ser	Pro	125 Ser	Val	Met	Δra	
۰,	, ,	🕶		1.0	u	٠.,	u	JC1	LCU	LCU	JUI		JUI	vui	1100	AT 9	

	130					135					140					
Leu 145		His	Thr	Gln	G1u 150	Pro	Gly	Glu	Trp	Leu 155	Glu	Leu	Leu	Leu	Glu 160	
Pro	Gly	Ser	Leu	Tyr 165	Ile	Leu	Arg	Gly	Ser 170	Ala	Arg	Tyr	Asp	Phe 175	Ser	
His	Glu	Ile	Leu 180	Arg	Asp	Glu	Glu	Ser 185	Phe	Phe	Gly	Glu	Arg 190	Arg	Ile	
Pro	Arg	Gly 195	Arg	Arg	Пe	Ser	Va1 200	Пe	Cys	Arg	Ser	Leu 205	Pro	Glu	Gly	
Met	Gly 210	Pro	Gly	Glu	Ser	Gly 215	Gln	Pro	Pro	Pro	Ala 220	Cys				
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						gat Asp										96
						act Thr			-	_	_		-		_	144
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96

482

85 90 95

ttg tag Leu *

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<211> 97

<212> PRT

<213> Homo sapiens

<400> 328

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Asn Leu Leu Ile Gly Ser Thr Ser Tyr Val Glu Glu Glu Met Pro Gln 35 40 45

Ile Glu Thr Arg Val Ile Leu Val Gln Glu Ala Gly Lys Gln Glu Glu 50 55 60

Leu Ile Lys Ala Leu Lys Asp Ile Lys Val Gly Phe Val Lys Met Glu 65 70 75 80

Ser Val Glu Glu Phe Glu Gly Leu Asp Ser Pro Glu Phe Glu Met Tyr 85 90 95

Leu

<210> 329

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ttc tgc ctc ctg tgg ccc ctc gtg gtg aag ggc tgc acg atg atc cgg Phe Cys Leu Leu Trp Pro Leu Val Val Lys Gly Cys Thr Met Ile Arg

20 25 30 tgg aag ata aac aac ctc att gcc tca gaa tcc tac tac acc tac gcc 144 Trp Lys Ile Asn Asn Leu Ile Ala Ser Glu Ser Tyr Tyr Thr Tyr Ala 35 40 tcc att tcc gga atc tcg agc atg cca tct ctg aga cat tcc agg atg 192 Ser Ile Ser Gly Ile Ser Ser Met Pro Ser Leu Arg His Ser Arg Met ggc tcc atg ttc agc tcc agg atg aca gag gac agg gct gaa ccc aag 240 Gly Ser Met Phe Ser Ser Arg Met Thr Glu Asp Arg Ala Glu Pro Lys 65 70 75 gaa gcc gtg gag aga cag ttg atg acc tga 270 Glu Ala Val Glu Arg Gln Leu Met Thr * <210> 330 <211> 89 <212> PRT <213> Homo sapiens <400> 330 Met Val Ser Ala Ser Val Phe Val Gly Leu Val Ile Phe Tyr Ile Ala 5 10 Phe Cys Leu Leu Trp Pro Leu Val Val Lys Gly Cys Thr Met Ile Arg 25 Trp Lys Ile Asn Asn Leu Ile Ala Ser Glu Ser Tyr Tyr Thr Tyr Ala Ser Ile Ser Gly Ile Ser Ser Met Pro Ser Leu Arg His Ser Arg Met Gly Ser Met Phe Ser Ser Arg Met Thr Glu Asp Arg Ala Glu Pro Lys 70 75 Glu Ala Val Glu Arg Gln Leu Met Thr 85

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gaa gat gat gca cgg agt gag tct agt act gaa tgg gac tta gat gga 144 Glu Asp Asp Ala Arg Ser Glu Ser Ser Thr Glu Trp Asp Leu Asp Gly 35 40 45

ttc agt gag ctg gac tct gag tca gga agt tca agt tct ttt tca gat

Phe Ser Glu Leu Asp Ser Glu Ser Gly Ser Ser Ser Ser Phe Ser Asp

50

60

gat gaa gtc tgg gtg caa gta gca cct cag cga aat gca cag gat cag
Asp Glu Val Trp Val Gln Val Ala Pro Gln Arg Asn Ala Gln Asp Gln
65 70 75 80

cag ggt tct ttg taa 255 Gln Gly Ser Leu *

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<211> 84

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<400> 332

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Arg Val Tyr Pro Ser Cys Leu Glu Pro Gly Gln Ser Phe Ile Thr Glu 20 25 30

Glu Asp Asp Ala Arg Ser Glu Ser Ser Thr Glu Trp Asp Leu Asp Gly 35 40 45

Phe Ser Glu Leu Asp Ser Glu Ser Gly Ser Ser Ser Phe Ser Asp 50 55 60

Asp Glu Val Trp Val Gln Val Ala Pro Gln Arg Asn Ala Gln Asp Gln

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Gln	Gly	Ser	Leu													
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ata		400>		+00	a+a	2+4	at a	222	+	.					- 4. 1	40
aly Mot	Glu	att Ile	Len	tyy Trn	Leu	aly Mot	Val	lve	Ser	Trn	ddl	acc	gga	gta	CTT	48
1	u.u	110	LCu	5	LCu	1100	V (4)	LJ 3	10	пр	7311	1 () (uly	15	Leu	
		agc														96
Met	Phe	Ser	Arg 20	Ser	Lys	lyr	Ala	Ser 25	Ala	Glu	Lys	Trp	_	Gly	Leu	
			20					23					30			
gcc	ttg	cgţ	ttc	ctt	aac	cac	ctt	acc	tcc	ttc	aag	gaa	agc	tat	gaa	144
		Arg														
		35					40					45				
act.	cag	atg	aat	ato	cta	tat	ant	can	ctt	ata	aaa	מרא	tta	ant	220	192
		Met														172
	50					55					60					
																0.40
		ggc Gly														240
65	Lys	uiy	110	vai	70	1113	Giu	1112	diy	75	пр	361	Lys	261.	80	
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tag																243
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<211> 80

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<213> Homo sapiens

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Ala	Leu	Arg 35	Phe	Leu	Asn	His	Leu 40	Thr	Ser	Phe	Lys	Glu 45		Tyr	Glu	
Thr	G1n 50	Met	Asn	Met	Leu	Tyr 55	Ser	Gln	Leu	Val	Glu 60	Ala	Leu	Ser	Asn	
Asn 65	Lys	Gly	Pro	Val	Phe 70	His	Glu	His	Gly	Tyr 75	Trp	Ser	Lys	Ser	Asp 80	
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								999 Gly 25								96
aca															o+	144
Ala	atg Met	gca Ala 35	aaa Lys	atg Met	agc Ser	aaa Lys	gtt Val 40	999 Gly	aaa Lys	gtt Val	gtg Val	ttc Phe 45	ccg Pro	aga Arg	Leu	
Ala cag	Met gat	Ala 35 aaa	Lys aaa	Met tac	Ser tat	Lys · gat	Val 40 aag	ggg Gly aaa Lys	Lys tac	Val caa	Val gta	Phe 45 ttc	Pro	Arg	Leu ctg	192

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65					70					75					80	
									tta Leu 90						Thr	288
									gtg Val		_			Lys	_	336
									ttt Phe							384
									gcc Ala	_						432
									cag Gln							480
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									ggt Gly			-				567
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Ile	Leu	Ala	Va1 20	Phe	Tyr	Pro	Phe	Val 25	Asp	Leu	Ile	Asp	Asn 30		Asn	
G1n	Thr	His 35		Tyr	Ala	Pro	Phe 40	Ile	Пe	Пe	Gly	Leu 45		Leu	Ala	
Leu	Gly		Phe	Ser	Phe	Thr		Asp	Thr	Trp	Ser		Ser	Ara	Glv	

	50					55					60					
Asp 65	Thr	Ala	Glu	Ile	Leu 70	Gly	Ser	Gly	Ala	G1 <i>y</i> 75	He	Ala	Cys	Gly	Ser 80	
His	Val	Thr	Tyr	Asn 85	Met	Gly	Leu	Val	Leu 90	Asp	Pro	Ser	Leu	Asp 95	Thr	
Leu	Pro	Leu	Ala 100	Gly	Pro	Pro	Ile	Thr 105	Val	Thr	Leu	Phe	Gly 110	Lys	Ala	
Ile	Leu	Arg 115	Пe	Leu	Пe	Gly	Met 120	Val	Phe	Val	Leu	Ile 125	Ile	Arg	Asp	
Val	Met 130	Lys	Lys	Ile	Thr	Ile 135	Pro	Leu	Ala	Cys	Lys 140	Пe	Phe	Asn	Ile	
Pro 145	Cys	Asp	Asp	Ile	Arg 150	Lys	Ala	Arg	Gln	His 155	Met	Glu	Val	Glu	Leu 160	
Pro	Tyr	Arg	Tyr	Ile 165	Thr	Tyr	Gly	Met	Val 170	Gly	Phe	Ser	Пе	Thr 175	Phe	
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						ggg Gly										48
						gtc Val			-							96
						gcg Ala										144
						gtg Val 55										192

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Tyr Leu Thr Ile Leu *
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Leu Leu Gly Phe Gln Phe Val Cys Pro Gln Pro Ser Thr Gln His Arg
Lys Val Pro Gln Arg Met Ala Ala Glu Gly Ala Pro Glu Asp Asp Gly
Gly Gly Gly Ala Pro Gly Val Trp Gly Ala Gly Ala Pro Ala Glu Gly
                        55
Tyr Leu Thr Ile Leu
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Met Pro Ala Lys Asp Thr Ser Ser Val Phe Ala Leu Ala Cys Ser Pro
1
                 5
                                      10
                                                          15
gcg ggg gct ccg tca tcc cct ggg gaa tgc ctc ggc ctg caa gac cgc
                                                                       96
Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg
             20
ata ccg cat tgg aac agg gaa acc acc tac ttc agc acc tcc ctc agc
                                                                      144
Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser
         35
                             40
                                                  45
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aag gtg gca ggt ccc aac aag cct tgc acc acg agg aag tgg cag tgg 192 Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp 50 55 cat tcg gga tat ggc tcc ctg gcc agc ttg tga 225 His Ser Gly Tyr Gly Ser Leu Ala Ser Leu * 65 <210> 342 <211> 74 <212> PRT <213> Homo sapiens <400> 342 Met Pro Ala Lys Asp Thr Ser Ser Val Phe Ala Leu Ala Cys Ser Pro Ala Gly Ala Pro Ser Ser Pro Gly Glu Cys Leu Gly Leu Gln Asp Arg 25 Ile Pro His Trp Asn Arg Glu Thr Thr Tyr Phe Ser Thr Ser Leu Ser 40 Lys Val Ala Gly Pro Asn Lys Pro Cys Thr Thr Arg Lys Trp Gln Trp 55 His Ser Gly Tyr Gly Ser Leu Ala Ser Leu 65 70 <210> 343 <211> 240 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(240) <400> 343 atg tgc atc acg cac ctg gac cac aaa gac tac atc ttc ctg ctg ctc 48 Met Cys Ile Thr His Leu Asp His Lys Asp Tyr Ile Phe Leu Leu Leu 10 atc ggc ttc tgc atc ttc gcc gcg gga act gtg gct gcc tgg ctc aca 96 Ile Gly Phe Cys Ile Phe Ala Ala Gly Thr Val Ala Ala Trp Leu Thr 20 25

												_	tcg Ser	-	-	144
													cgg Arg			192
													ctt Leu			240
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Met		<001 ALT		His	l eu	Asn	His	Lvs	Δsn	Tyr	בוז	Pho	Leu	ريم ا	ريو ا	
1				5					10					15		
Ile	Gly	Phe	Cys 20	He	Phe	Ala	Ala	Gly 25	Thr	Val	Ala	Ala	Trp 30	Leu	Thr	
Gly	Val	Cys 35	Ala	Val	Leu	Tyr	Gln 40	Asn	Thr	Arg	His	Lys 45	Ser	Ser	Glu	
Glu	Asp 50		Asp	Glu	Ala	Gly 55		Arg	Val	Glu	Val 60		Arg	Arg	Ile	
Phe 65		Thr	Gln	Thr	Ser 70		Val	Gln	Glu	Phe 75		Gln	Leu	Пе		
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agg Arg	ttt Phe	gcc Ala 35	ttt Phe	tcc Ser	gtg Val	tct Ser	gtg Val 40	ctg Leu	gac Asp	ctt Leu	gac Asp	ctc Leu 45	aag Lys	ccc Pro	tac Tyr		144
gag Glu	agc Ser 50	att Ile	ccc Pro	cat His	cag Gln	tat Tyr 55	aaa Lys	ctg Leu	gac Asp	ggc Gly	aag Lys 60	atc Ile	gtc Val	aac Asn	tat Tyr		192
tat Tyr 65	tca Ser	aag Lys	act Thr	gta Val	cgt Arg 70	gcc Ala	aaa Lys	gac Asp	aac Asn	gcc Ala 75	gtg Val	atg Met	tcg Ser	act Thr	cgg Arg 80		240
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<213> Homo sapiens

<400> 346

 Met
 Thr
 Ala
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 Asp
 Cys
 Ser
 Ile
 Met
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 Ala
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 Ser
 Pro
 Cys
 Leu

 Gln
 Asp
 Ala
 Ser
 Ser
 Asp
 Gln
 Arg
 Pro
 Val
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<212> DNA

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									ctg Leu 45				144
									gac Asp	-			192
									tac Tyr				240
									tcc Ser				288
							Phe		gcg Ala				336
Asn		Gly			Thr				ggc Gly 125				384
									gga Gly				432
				aaa Lys					tat Tyr	tga *			474

495

145 150 155 <210> 348 <211> 157 <212> PRT <213> Homo sapiens <400> 348 Met Glu Ala Leu Arg Arg Ala His Glu Val Ala Leu Arg Leu Leu Leu Cys Arg Pro Trp Ala Ser Arg Ala Ala Ala Arg Pro Lys Pro Ser Ala 25 Ser Glu Val Leu Thr Arg His Leu Leu Gln Arg Arg Leu Pro His Trp 40 Thr Ser Phe Cys Val Pro Tyr Ser Ala Val Arg Asn Asp Gln Phe Gly 55 Leu Ser His Phe Asn Trp Pro Val Gln Gly Ala Asn Tyr His Val Leu Arg Thr Gly Cys Phe Pro Phe Ile Lys Tyr His Cys Ser Lys Ala Pro Trp Gln Asp Leu Ala Arg Gln Asn Arg Phe Phe Thr Ala Leu Lys Val 100 105 Val Asn Leu Gly Ile Pro Thr Leu Leu Tyr Gly Leu Gly Ser Trp Leu 120 125 Phe Ala Arg Val Thr Glu Thr Val His Thr Ser Tyr Gly Pro Ile Thr 135 Val Tyr Phe Leu Asn Lys Glu Asp Glu Gly Ala Met Tyr 145 150 <210> 349

<211> 288

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			aag Lys								96
			agg Arg							1	.44
			ctc Leu 55							1	.92
			tta Leu			-	_			2	240
		-	gga Gly					~	tga *	2	288 .

<210> 350

<211> 95

<212> PRT

<213> Homo sapiens

<400> 350

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                                     10
tcc ctg ggg cag ctg cag ggg ctc acg gac cca tca ggg tct cca cag
                                                                       96
Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
             20
                                 25
ctc ccc tgc agt gtg tgc acc cca caa tgt ctg cgg ctc ttc ttc cgg
                                                                      144
Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
         35
                             40
cgt gtc ggg ctt tga
                                                                      159
Arg Val Gly Leu *
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Met Cys Leu Arg Val Phe Thr Leu Ala Leu Ser Cys Leu Leu Cys Gly
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Ser Leu Gly Gln Leu Gln Gly Leu Thr Asp Pro Ser Gly Ser Pro Gln
Leu Pro Cys Ser Val Cys Thr Pro Gln Cys Leu Arg Leu Phe Phe Arg
        35
Arg Val Gly Leu
   50
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     <221> CDS
     <222> (1)...(210)
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<213> Homo sapiens

-	ggt Gly		atg												-	48
	tta Leu			_												96
	atg Met															144
-	cta Leu 50	_												_		192
	gaa Glu				tag *											210
	<2 <2	210> 211> 212> 213>	69	sar	oiens	5		٠								
		100>				•	3 51		_		D.I.	0.7		0.7	0	
Met 1	Gly	Ala	Met	Asn 5	HIS	Asp	Inr	Asn	Tyr 10	Ser	Phe	Gin	Val	15	Cys	
Gly	Leu	Ile	Va1 20	Val	Ala	Tyr	Lys	Asp 25	Gly	Ser	Pro	Ala	His 30	Pro	His	*
Phe	Met	Asp 35		Glu	Leu	Cys	Ser 40		Tyr	Trp	Thr	Lys 45		Leu	Leu	
Arg	Leu 50		Glu	Tyr	Thr	G1u 55	-	Lys	Lys	Asn	G1n 60		Ile	Gln	Lys	
Pro 65	Glu	Tyr	Ser	Glu												
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      <221> misc feature
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atg gtc ctg ccg gtg gca gcc tat ggn ctg atc ctg atg gcc atg ctg
                                                                       48
Met Val Leu Pro Val Ala Ala Tyr Xaa Leu Ile Leu Met Ala Met Leu
 1
                 5
                                                          15
tgg cgc ggc ctg gcc cag ggc ggg agt gcc ggc tgg ggc gcg ctg ctc
                                                                       96
Trp Arg Gly Leu Ala Gln Gly Gly Ser Ala Gly Trp Gly Ala Leu Leu
                                 25
ttc acg ctc tct gat ggc gtg ctg gcc tgg gac acc ttc gcc cag ccc
                                                                      144
Phe Thr Leu Ser Asp Gly Val Leu Ala Trp Asp Thr Phe Ala Gln Pro
         35
ctg ccc cat gcc cgc ctg gtg atc atg acc acc tac tat gct gcc cag
                                                                      192
Leu Pro His Ala Arg Leu Val Ile Met Thr Thr Tyr Tyr Ala Ala Gln
     50
                         55
                                             60
ctc ctc atc aca ctg tca gcc ctc agg agc ccg gtg ccc aag act gac
                                                                      240
Leu Leu Ile Thr Leu Ser Ala Leu Arg Ser Pro Val Pro Lys Thr Asp
 65
                     70
                                         75
                                                              80
tga
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<210> 358
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<211> 80

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<213> Homo sapiens

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Trp	Arg	Gly	Leu 20	Ala	Gln	Gly	Gly	Ser 25	Aļa	Gly	Trp	Gly	A1a 30	Leu	Leu	
Phe	Thr	Leu 35	Ser	Asp	Gly	Val	Leu 40	Ala	Trp	Asp	Thr	Phe 45	Ala	Gln	Pro	
Leu	Pro 50	His	Ala	Arg	Leu	Va1 55	Ile	Met	Thr	Thr	Tyr 60	Tyr	Ala.	Ala	Gln	
Leu 65	Leu	Ile	Thr	Leu	Ser 70	Ala	Leu	Arg	Ser	Pro 75	Val	Pro	Lys	Thr	Asp 80	
	<2 <2	210> 211> 212> 213>	324 DNA	o sap	oiens											
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atg		400> agc		tgt	ggt	tcc	ctt	ata	gcc	atq	agt	gtt	ata	ata	gga	48
											Ser					
											cgt Arg					96
											atg Met	-		-		144
											agc Ser 60					192
											caa Gln					240
agt	tgg	gca	gga	aga	ctc	att	ctg	agt	gta	gat	ggc	tct	999	ttt	tgt	288

WO 01/29221

PCT/US00/29052

96

502

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Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
gag agg gtg aaa tot ttg gto gtt aaa caa tto tag
                                                                      324
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe *
                                105
            100
      <210> 360
      <211> 107
      <212> PRT
      <213> Homo sapiens
      <400> 360
Met Lys Ser Thr Cys Gly Ser Leu Val Ala Met Ser Val Val Val Gly
                                    10
Pro Ala Ser Ser Ala Arg Asp Leu Pro Ser Pro Arg Gly Tyr Thr Met
                                25
Thr Pro Gln Thr Met Lys Val Asp Glu Glu Val Met Ala Phe Arg Gly
                            40
Ala Arg Cys Asp Gly Ile Arg Val Leu Pro Ser Ser Val Glu Asp Thr
Pro Ala Leu Lys Arg Ala Lys Ser Ser Lys Thr Gln Pro Thr Gly Asp
                    70
                                        75
Ser Trp Ala Gly Arg Leu Ile Leu Ser Val Asp Gly Ser Gly Phe Cys
Glu Arg Val Lys Ser Leu Val Val Lys Gln Phe
            100
                                105
      <210> 361
      <211> 252
      <212> DNA
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      <221> CDS
      <222> (1)...(252)
      <400> 361
                                                                       48
atg gag gaa gga ggc ggc ggc gta cgg agt ctg gtc ccg ggc ggg ccg
Met Glu Glu Gly Gly Gly Val Arg Ser Leu Val Pro Gly Gly Pro
                 5
                                     10
```

gtg tta ctg gtc ctc tgc ggc ctc ctg gag gcg tcc ggc ggc ggc cga

Val	Leu	Leu	Va1 20	Leu	Cys	Gly	Leu	Leu 25	Glu	Ala	Ser	Gly	Gly 30	Gly	Arg	
-	ctt Leu				-	-	-				-	-		~ ~		144
	acc Thr 50															192
	tat Tyr									-						240
	aaa Lys		taa *													252
	<2 <2	210> 211> 212> 213>	83	sap	oiens	5										
Met 1	Glu	100> G1u		G1 <i>y</i> 5	Gly	G1 y	Val	Arg	Ser	Leu	Val	Pro	Gly	Gly 15	Pro	
	Leu		20			•		25				_	30	Gly		
Ala	Leu	Pro	Gln	Leu	Ser	Asp	Asp	Пe	Pro	Phe	Arg	Val	Asn	Trp	Pro	

35 40 45 Gly Thr Glu Phe Ser Leu Pro Thr Thr Gly Val Leu Tyr Lys Glu Asp

Asn Tyr Val Ile Met Thr Thr Ala His Lys Glu Lys Tyr Lys Lys

75

80

55

70

<210> 363 <211> 459

Lys Lys Asn

<212> DNA

<213> Homo sapiens

<220> <221> CDS <222> (1)...(459) <400> 363 atg gat gga aca caa cag cag att ttt aaa atg tta gca gag gta cta 48 Met Asp Gly Thr Gln Gln Gln Ile Phe Lys Met Leu Ala Glu Val Leu 5 1 10 15 gga gga atc aat tgt gta aaa gcc tcg gtt ctt acg cct tat tac cac 96 Gly Gly Ile Asn Cys Val Lys Ala Ser Val Leu Thr Pro Tyr Tyr His aaa gta gat ttt gag tgt atc ttg gat aaa aga aaa acct ctt ccg 144 Lys Val Asp Phe Glu Cys Ile Leu Asp Lys Arg Lys Lys Pro Leu Pro 35 tat gga agc cat aat ata gca ttg gga caa cta cca gaa atg ccc tgg 192 Tyr Gly Ser His Asn Ile Ala Leu Gly Gln Leu Pro Glu Met Pro Trp 50 55 gaa tca aat atc gaa ata gtt gga tca agg ctg cca cca ggg gct gaa 240 Glu Ser Asn Ile Glu Ile Val Gly Ser Arg Leu Pro Pro Gly Ala Glu 65 70 agg att gct ttg gaa ttt ttg gat tca aaa gca ctt tgt aga aat atc 288 Arg Ile Ala Leu Glu Phe Leu Asp Ser Lys Ala Leu Cys Arg Asn Ile 85 90 cct cac atg aaa gga aaa tct gct atg aaa aaa cga cat ttg gaa att 336 Pro His Met Lys Gly Lys Ser Ala Met Lys Lys Arg His Leu Glu Ile 100 105 ctg ggg tat cgt gta att cag att tcc cag ttt gaa tgg aac tct atg 384 Leu Gly Tyr Arg Val Ile Gln Ile Ser Gln Phe Glu Trp Asn Ser Met 115 120 125 gca ctg tca aca aag gat gct cgg atg gac tac ctg aga gaa tgt ata 432 Ala Leu Ser Thr Lys Asp Ala Arg Met Asp Tyr Leu Arg Glu Cys Ile 130 135 140 ttt gga gaa gtc aag tca tgt ttg tag 459 Phe Gly Glu Val Lys Ser Cys Leu * 145 150

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<210> 364
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Gly Gly Ile Asn Cys Val Lys Ala Ser Val Leu Thr Pro Tyr Tyr His
                                 25
Lys Val Asp Phe Glu Cys Ile Leu Asp Lys Arg Lys Lys Pro Leu Pro
Tyr Gly Ser His Asn Ile Ala Leu Gly Gln Leu Pro Glu Met Pro Trp
Glu Ser Asn Ile Glu Ile Val Gly Ser Arg Leu Pro Pro Gly Ala Glu
                    70
Arg Ile Ala Leu Glu Phe Leu Asp Ser Lys Ala Leu Cys Arg Asn Ile
Pro His Met Lys Gly Lys Ser Ala Met Lys Lys Arg His Leu Glu Ile
                                 105
Leu Gly Tyr Arg Val Ile Gln Ile Ser Gln Phe Glu Trp Asn Ser Met
                            120
Ala Leu Ser Thr Lys Asp Ala Arg Met Asp Tyr Leu Arg Glu Cys Ile
                        135
Phe Gly Glu Val Lys Ser Cys Leu
145
                    150
      <210> 365
      <211> 600
      <212> DNA
      <213> Homo sapiens
      <220>
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      <222> (1)...(600)
      <400> 365
atg gtg tgg cgc cgg ctt ctg cgg aag agg tgg gtg ctc gcc ctg gtc
                                                                       48
Met Val Trp Arg Arg Leu Leu Arg Lys Arg Trp Val Leu Ala Leu Val
ttc ggg ctg tcg ctc gtc tac ttc ctc agc agc acc ttc aag cag gag
                                                                       96
```

Phe	Gly	Leu	Ser 20	Leu	Val	Tyr	Phe	Leu 25	Ser	Ser	Thr	Phe	Lys 30	Gln	Glu	
				_	-					-	_		-	cat His		144
-			-										_	agt Ser	-	192
														atc Ile		240
-	_				_				_	-	_	-	-	aat Asn 95		288
-	_		-		-		_	-	_	_		-	_	gat Asp	~ ~	336
														tcc Ser	-	384
_	_	_			_				-		_			aac Asn		432
_	-	-	-		_				_	-	-	-	-	cac His		480
	_	-	_	_		-					_	-		cag Gln 175		528
gag Glu								_	_		-		-		-	576
ccg	ссс	gag	ctc	ttc	ссс	gct	tga									600

507 .

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Pro Pro Glu Leu Phe Pro Ala *
        195
      <210> 366
      <211> 199
      <212> PRT
      <213> Homo sapiens
      <400> 366
Met Val Trp Arg Arg Leu Leu Arg Lys Arg Trp Val Leu Ala Leu Val
                                    10
Phe Gly Leu Ser Leu Val Tyr Phe Leu Ser Ser Thr Phe Lys Gln Glu
Glu Arg Ala Val Arg Asp Arg Asn Leu Leu Gln Val His Asp His Asn
                            40
Gln Pro Ile Pro Trp Lys Val Gln Phe Asn Leu Gly Asn Ser Ser Arg
                        55
Pro Ser Asn Gln Cys Arg Asn Ser Ile Gln Gly Lys His Leu Ile Thr
                                        75
Asp Glu Leu Gly Tyr Val Cys Glu Arg Lys Asp Leu Leu Val Asn Gly
                                    90
Cys Cys Asn Val Asn Val Pro Ser Thr Lys Gln Tyr Cys Cys Asp Gly
                                105
Cys Trp Pro Asn Gly Cys Cys Ser Ala Tyr Glu Tyr Cys Val Ser Cys
                           120
Cys Leu Gln Pro Asn Lys Gln Leu Leu Leu Glu Arg Phe Leu Asn Arg
                       135
                                            140
Ala Ala Val Ala Phe Gln Asn Leu Phe Met Ala Val Glu Asp His Phe
                    150
Glu Leu Cys Leu Ala Lys Cys Arg Thr Ser Ser Gln Ser Val Gln His
               165
                                    170
Glu Asn Thr Tyr Arg Asp Pro Ile Ala Lys Tyr Cys Tyr Gly Glu Ser
           180
                                185
Pro Pro Glu Leu Phe Pro Ala
        195
     <210> 367
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<222> (1)...(249)

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<210> 368

<211> 82

<212> PRT

<213> Homo sapiens

<400> 368

 Met Ser Lys
 Tyr Lys
 His Lys
 Ser Ser Pro Leu Leu Pro Leu Leu Pro Leu Leu Ile
 1
 15

 Phe His Asn Val Cys
 Phe Ser Pro Ala Asn Lys
 Pro Lys
 Ile Leu Ala 30

 Asn Glu Lys
 Val Ile Thr Val Leu Ala Ala Cys
 Leu Glu Ser Glu Asn 45

 Gln Asn Ala Gln Arg Ile Gly Ala Ala Ala Leu Gly Ser Asp Leu Gln 50
 55
 60

 Leu Ser Glu Gly Lys
 Asn Ser Phe Glu Lys
 Pro Ile Ser Lys
 Lys Lys

 65
 70
 75
 80

Ser Gly

<210> 369 <211> 285 <212> DNA <213> Homo sapiens <220> <221> CDS <222> (1)...(285) <400> 369 atg gac ggc cgc ggg gct ttc tgg aca gtg gcc att ccc aga gcc agg 48 Met Asp Gly Arg Gly Ala Phe Trp Thr Val Ala Ile Pro Arg Ala Arg 10 cag gaa ggc ctc ggg agg ctg ggg ctc ccg ttc ccg gtg aag cgg acg 96 Gln Glu Gly Leu Gly Arg Leu Gly Leu Pro Phe Pro Val Lys Arg Thr 20 25 ccg cca gcg ccc cag aac cca gga gga agc aca cag gcc cca cag aga 144 Pro Pro Ala Pro Gln Asn Pro Gly Gly Ser Thr Gln Ala Pro Gln Arg 40 gtg gtt ggc aag agt cac tcg ggg att agg atg ccg gcc aaa tcg cgg 192 Val Val Gly Lys Ser His Ser Gly Ile Arg Met Pro Ala Lys Ser Arg 50 55 aat ttg agg ctg gaa tcc aag ctc aac agg act gct gtg tgt gaa gca 240 Asn Leu Arg Leu Glu Ser Lys Leu Asn Arg Thr Ala Val Cys Glu Ala 65 70 75 ctc aag agg gcc cct aca acc aac ctg cca gga gtc ggc tcc tga 285 Leu Lys Arg Ala Pro Thr Thr Asn Leu Pro Gly Val Gly Ser * 85

<210> 370

<211> 94

<212> PRT

<213> Homo sapiens

<400> 370

Met 1	Asp	Gly	Arg	Gly 5	Ala	Phe	Trp	Thr	Val 10	Ala	Ile	Pro	Arg	Ala 15	Arg	
Gln	Glu	Gly	Leu 20	Gly	Arg	Leu	Gly	Leu 25	Pro	Phe	Pro	۷a٦	Lys 30	Arg	Thr	
Pro	Pro	A1 a 35	Pro	Gln	Asn	Pro	Gly 40	Gly	Ser	Thr	Gln	Ala 45	Pro	Gln	Arg	
Val	Va1 50	Gly	Lys	Ser	His	Ser 55	Gly	Ile	Arg	Met	Pro 60	Ala	Lys	Ser	Arg	
65	Leu	•			70	•			_	75			•	Glu	A1a 80	
Leu	Lys	Arg	Ala	Pro 85	Thr	Thr	Asn	Leu	Pro 9 0	Gly	Val	Gly	Ser			
	<2 <2	210> 211> 212> 213>	249	o sap	oiens	5										
	<2	220> 221> 222>	CDS	(2	249)											
atg	</td <td>100> gac</td> <td></td> <td>gac</td> <td>atc</td> <td>aac</td> <td>gac</td> <td>gac</td> <td>gaa</td> <td>ttc</td> <td>ctg</td> <td>cac</td> <td>ctg</td> <td>ccg</td> <td>gcg</td> <td>48</td>	100> gac		gac	atc	aac	gac	gac	gaa	ttc	ctg	cac	ctg	ccg	gcg	48
Met 1	Arg	Asp	Cys	Asp 5	Ile	Asn	Asp	Asp	Glu 10	Phe	Leu	His	Leu	Pro 15	Ala	
	ttg Leu															96
	ctc Leu															144
gtg Val	gac Asp 50															192
gac Asp 65																240
ccg	aga	tga														249

WO 01/29221 PCT/US00/29052

511

Pro Arg *

<210> 372

<211> 82

<212> PRT

<213> Homo sapiens

<400> 372

Met Arg Asp Cys Asp Ile Asn Asp Asp Glu Phe Leu His Leu Pro Ala 1 5 10 15

His Leu Arg Val Val Gly Pro Gln Gln Leu His Ser Glu Thr Asn Glu 20 25 30

Arg Leu Phe Asp Glu Lys Tyr Lys Pro Val Val Leu Thr Asp Asp Gln 35 40 45

Val Asp Gln Ala Leu Trp Glu Glu Gln Val Leu Gln Lys Glu Lys Lys 50 55 60

Asp Arg Leu Ala Leu Ser Gln Ala His Ser Leu Val Gln Ala Glu Ala 65 70 75 80

Pro Arg

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<211> 219

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<213> Homo sapiens

<220>

<221> CDS

<222> (1)...(219)

<221> misc_feature

<222> (1)...(219)

<223> n = A.T.C or G

<400> 373

atg ggc cga gcg ctg ccc ccc ggg ggt cct cgg cgc cgg gcg can tta Met Gly Arg Ala Leu Pro Pro Gly Gly Pro Arg Arg Arg Ala Xaa Leu 1 5 10

48

96

nga gcg can gca gca ggc tcc att ccc ggc cgc cgc cgc tca gcc cat Xaa Ala Xaa Ala Ala Gly Ser Ile Pro Gly Arg Arg Arg Ser Ala His

20 25 30

```
tac gca aac ctg gcg ggt cca acc aac ccc gct ctg ccg ccg ctg ctg
                                                                      144
Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu
         35
gaa ccc agg agg cgt gct tgc agg ctt cgg gca cta cgc ggg gct gga
                                                                      192
Glu Pro Arg Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly
                         55
                                              60
aat acc acg cac tgc ccc ttc gcc tag
                                                                      219
Asn Thr Thr His Cys Pro Phe Ala *
 65
                     70
      <210> 374
      <211> 72
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      <213> Homo sapiens
      <220>
      <221> VARIANT
      <222> (1)...(72)
      <223> Xaa = Any Amino Acid
      <400> 374
Met Gly Arg Ala Leu Pro Pro Gly Gly Pro Arg Arg Ala Xaa Leu
                 5
                                    10
Xaa Ala Xaa Ala Ala Gly Ser Ile Pro Gly Arg Arg Arg Ser Ala His
                                25
Tyr Ala Asn Leu Ala Gly Pro Thr Asn Pro Ala Leu Pro Pro Leu Leu
                            40
Glu Pro Arg Arg Arg Ala Cys Arg Leu Arg Ala Leu Arg Gly Ala Gly
                        55
                                            60
Asn Thr Thr His Cys Pro Phe Ala
65
                    70
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      <211> 579
      <212> DNA
      <213> Homo sapiens
      <220>
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      <222> (1)...(579)
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													375	400>	<	
48													aag Lys			
96												Val	gtg Val 20			
144		_	_	-	_	_		_			-	-	gct Ala			-
192													gcc Åla			
240													gcc Ala		Trp	
288													aat Asn			
336	_											-	ctg Leu 100			
384													ggt Gly			
432				Trp		Gly	Tyr	Thr	Asn	Ala	Thr	Phe	gtc Val	Ala	Val	Пe
480													gtg Val			
528													ccg Pro			

agc tgg gct tac tgc cgg gcc ctg cat aca cag cgc ctc cag tgg gag
Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu
180

tga
*

170

175

576

577

<210> 376 <211> 192 <212> PRT <213> Homo sapiens

<400> 376

Met Ala Pro Lys Pro Gly Ala Glu Trp Ser Thr Ala Leu Ser His Leu 10 Val Leu Gly Val Val Ser Leu His Ala Ala Val Ser Thr Ala Glu Ala Ser Arg Gly Ala Ala Ala Gly Phe Leu Leu Gln Val Leu Ala Ala Thr 40 Thr Thr Leu Ala Pro Gly Leu Ser Thr His Glu Asp Cys Leu Ala Gly 55 Ala Trp Val Ala Thr Val Ile Gly Leu Pro Leu Leu Ala Phe Asp Phe His Trp Val Asn Gly Asp Arg Ser Ser Ala Asn Leu Leu Gly Gly 90 Gly Met Val Leu Ala Val Ala Gly Gly His Leu Gly Pro Glu Gly Arg 105 Ser Val Ala Gly Gln Ala Met Leu Leu Val Val Ala Val Thr Ile Leu 120 Ile Val Ala Val Phe Thr Ala Asn Thr Tyr Gly Met Trp Gly Gly Ala 135 140 Met Leu Gly Val Ala Gly Leu Leu Ser Arg Leu Glu Glu Asp Arg Leu 150 155 160 Leu Leu Pro Lys Glu Asp Val Cys Arg Trp Ala Leu Ala Val Gly 170 Ser Trp Ala Tyr Cys Arg Ala Leu His Thr Gln Arg Leu Gln Trp Glu 180 185 190

<210> 377 <211> 606

		212> 213>			pien	S										
	<	220> 221> 222>	CDS		606)											
	acc		cag				gcc Ala									48
							gcg Ala									96
							agg Arg 40									144
							cgg Arg									192
							gac Asp									240
							tcc Ser									288
							ctg Leu									336
ggc 31y	cag Gln	ctc Leu 115	acc Thr	ttc Phe	ctc Leu	ctg Leu	99 <u>9</u> Gly 120	ctg Leu	gtg Val	ggc Gly	ctg Leu	ccc Pro 125	ctg Leu	ctg Leu	tca Ser	384
							gag Glu			-	-	-			_	432

gcg agt ttt gtc ctg gtc atc ggg ctc gtg act ttc tac aga att ggc Ala Ser Phe Val Leu Val Ile Gly Leu Val Thr Phe Tyr Arg Ile Gly 145 150 150 160	480
cca tac acc aac ctg tcc tgg tcc tgc tac ctg aac att ggc gcc tgc Pro Tyr Thr Asn Leu Ser Trp Ser Cys Tyr Leu Asn Ile Gly Ala Cys 165 170 175	528
ctt ctg gcc acg ctg gcg gca gca tgc tca tct gga aca ttc tcc aca Leu Leu Ala Thr Leu Ala Ala Ala Cys Ser Ser Gly Thr Phe Ser Thr 180 185 190	576
aga ggg agg act gca tgg ccc ccc ggg tga Arg Gly Arg Thr Ala Trp Pro Pro Gly * 195 200	606
<210> 378 <211> 201 <212> PRT <213> Homo sapiens	
<400> 378 Mot The Val Cle Arg Lou Val Ala Ala Ala Val Lou Val Ala Lou Val	
THE COUNTY OF THE AND LED VOLATO AND AND AND LED VOLATO AND LED VOL	
Met Thr Val Gln Arg Leu Val Ala Ala Ala Val Leu Val Ala Leu Val 1	
1 5 10 15 Ser Leu Ile Leu Asn Asn Val Ala Ala Phe Thr Ser Asn Trp Val Cys 20 25 30	
1 5 10 15 Ser Leu Ile Leu Asn Asn Val Ala Ala Phe Thr Ser Asn Trp Val Cys	
Ser Leu Ile Leu Asn Asn Val Ala Ala Phe Thr Ser Asn Trp Val Cys 20 25 30 Gln Thr Leu Glu Asp Gly Arg Arg Arg Ser Val Gly Leu Trp Arg Ser 35 40 Cys Trp Leu Val Asp Arg Thr Arg Gly Gly Pro Ser Pro Gly Ala Arg	
1 5 10 15 Ser Leu Ile Leu Asn Asn Val Ala Ala Phe Thr Ser Asn Trp Val Cys 20 25 30 Gln Thr Leu Glu Asp Gly Arg Arg Arg Ser Val Gly Leu Trp Arg Ser 35 40 45 Cys Trp Leu Val Asp Arg Thr Arg Gly Gly Pro Ser Pro Gly Ala Arg 50 55 60 Ala Gly Gln Val Asp Ala His Asp Cys Glu Ala Leu Gly Trp Gly Ser	
Ser Leu Ile Leu Asn Asn Val Ala Ala Phe Thr Ser Asn Trp Val Cys 20 25 30 Gln Thr Leu Glu Asp Gly Arg Arg Arg Ser Val Gly Leu Trp Arg Ser 35 40 Cys Trp Leu Val Asp Arg Thr Arg Gly Gly Pro Ser Pro Gly Ala Arg 50 55 60 Ala Gly Gln Val Asp Ala His Asp Cys Glu Ala Leu Gly Trp Gly Ser 65 70 75 80 Glu Ala Ala Gly Phe Gln Glu Ser Arg Gly Thr Val Lys Leu Gln Phe	
Ser Leu Ile Leu Asn Asn Val Ala Ala Phe Thr Ser Asn Trp Val Cys 20 25 30 Gln Thr Leu Glu Asp Gly Arg Arg Arg Ser Val Gly Leu Trp Arg Ser 35 40 45 Cys Trp Leu Val Asp Arg Thr Arg Gly Gly Pro Ser Pro Gly Ala Arg 50 55 60 Ala Gly Gln Val Asp Ala His Asp Cys Glu Ala Leu Gly Trp Gly Ser 65 70 75 80 Glu Ala Ala Gly Phe Gln Glu Ser Arg Gly Thr Val Lys Leu Gln Phe 85 90 95 Asp Met Met Arg Ala Cys Asn Leu Val Ala Thr Ala Ala Leu Thr Ala	
Ser Leu Ile Leu Asn Asn Val Ala Ala Phe Thr Ser Asn Trp Val Cys 20 25 30 Gln Thr Leu Glu Asp Gly Arg Arg Arg Ser Val Gly Leu Trp Arg Ser 35 40 45 Cys Trp Leu Val Asp Arg Thr Arg Gly Gly Pro Ser Pro Gly Ala Arg 50 55 60 Ala Gly Gln Val Asp Ala His Asp Cys Glu Ala Leu Gly Trp Gly Ser 65 70 75 80 Glu Ala Ala Gly Phe Gln Glu Ser Arg Gly Thr Val Lys Leu Gln Phe 85 90 95 Asp Met Met Arg Ala Cys Asn Leu Val Ala Thr Ala Ala Leu Thr Ala 100 105 110 Gly Gln Leu Thr Phe Leu Leu Gly Leu Val Gly Leu Pro Leu Leu Ser	
Ser Leu Ile Leu Asn Asn Val Ala Ala Phe Thr Ser Asn Trp Val Cys 20 25 30 30 Gln Thr Leu Glu Asp Gly Arg Arg Arg Ser Val Gly Leu Trp Arg Ser 35 40 45 Ser Pro Gly Ala Arg 50 55 60 Ala Gly Gln Val Asp Ala His Asp Cys Glu Ala Leu Gly Trp Gly Ser 65 70 75 80 Glu Ala Ala Gly Phe Gln Glu Ser Arg Gly Thr Val Lys Leu Gln Phe 85 90 95 Asp Met Met Arg Ala Cys Asn Leu Val Ala Thr Ala Ala Leu Thr Ala 100 105 110	
1	
Ser Leu Ile Leu Asn Asn Val Ala Ala Phe Thr Ser Asn Trp Val Cys 20 25 30 Gln Thr Leu Glu Asp Gly Arg Arg Arg Ser Val Gly Leu Trp Arg Ser 35 40 45 Cys Trp Leu Val Asp Arg Thr Arg Gly Gly Pro Ser Pro Gly Ala Arg 50 55 60 Ala Gly Gln Val Asp Ala His Asp Cys Glu Ala Leu Gly Trp Gly Ser 65 70 75 80 Glu Ala Ala Gly Phe Gln Glu Ser Arg Gly Thr Val Lys Leu Gln Phe 85 90 95 Asp Met Met Arg Ala Cys Asn Leu Val Ala Thr Ala Ala Leu Thr Ala 100 105 110 Gly Gln Leu Thr Phe Leu Leu Gly Leu Val Gly Leu Pro Leu Leu Ser 115 120 125 Pro Asp Ala Pro Cys Trp Glu Glu Ala Met Ala Ala Ala Phe Gln Leu	

Lou	1	. 67-	Thu	165		۸٦.	۸٦ -	0	170		0.7	-T-1	DI.	175		
			180					185	•	' Ser	· Gly	ınr	190		Thr	
Arg	Gly	Arg 195	Thr	Ala	Trp	Pro	Pro 200		•							
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	gnc		379 acg Thr													48
			aga Arg 20													96
			aaa Lys													144
			gga Gly													192
tgt Cys 65	gga Gly	gag Glu	cag Gln	cgg Arg	gga Gly 70	gag Glu	gac Asp	tgt Cys	gcc Ala	gag Glu 75	ctg Leu	cat His	gac Asp	tac Tyr	ttc Phe 80	240
aat Asn	gtc Val	ctg Leu	agt Ser	tac Tyr 85	aga Arg	agc Ser	ctg Leu	ggt Gly	aac Asn 90	tgc Cys	agc Ser	ttc Phe	ttc Phe	aca Thr 95	gag Glu	288

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act ggt tag
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                                25
Leu Arg Arg Lys Ser Ala Gly Gln Glu Glu Trp Ser Pro Ser Ala Pro
Ser Pro Pro Gly Ser Cys Val Gln Ala Glu Ala Ala Pro Ala Gly Leu
Cys Gly Glu Gln Arg Gly Glu Asp Cys Ala Glu Leu His Asp Tyr Phe
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                                        75
Asn Val Leu Ser Tyr Arg Ser Leu Gly Asn Cys Ser Phe Phe Thr Glu
                85
                                    90
Thr Gly
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                                                                       48
Met Ala Val Leu Val Leu Arg Leu Thr Val Val Leu Gly Leu Leu Val
 1
                                     10
                                                         15
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Lys Pro Asp Asp Ser Gly Lys Asp Pro Lys Pro Asp Phe Pro Lys Phe 35 40 45 cta agc ctc ctg ggc aca gag atc att gag aat gca gtc gag ttc atc Leu Ser Leu Leu Gly Thr Glu Ile Ile Glu Asn Ala Val Glu Phe Ile 50 55 60 ctc cgc tcc atg tcc agg agc aca gga ttt atg gaa ttt gat gat aat Leu Arg Ser Met Ser Arg Ser Thr Gly Phe Met Glu Phe Asp Asp Asn 65 70 75 80 gaa gga aaa cat tca tca aag tga Glu Gly Lys His Ser Ser Lys *	96
Leu Ser Leu Leu Gly Thr Glu Ile Ile Glu Asn Ala Val Glu Phe Ile 50 ctc cgc tcc atg tcc agg agc aca gga ttt atg gaa ttt gat gat aat Leu Arg Ser Met Ser Arg Ser Thr Gly Phe Met Glu Phe Asp Asp Asn 65 70 75 80 gaa gga aaa cat tca tca aag tga Glu Gly Lys His Ser Ser Lys * 85	14
Leu Arg Ser Met Ser Arg Ser Thr Gly Phe Met Glu Phe Asp Asp Asn 65 70 75 80 gaa gga aaa cat tca tca aag tga Glu Gly Lys His Ser Ser Lys * 85)2
Glu Gly Lys His Ser Ser Lys * 85	. 0
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Met Ala Val Leu Val Leu Arg Leu Thr Val Val Leu Gly Leu Leu Val 1 5 10 15	
Leu Phe Leu Thr Cys Tyr Ala Asp Asp Lys Pro Asp Lys Pro Asp Asp 20 25 30	
Lys Pro Asp Asp Ser Gly Lys Asp Pro Lys Pro Asp Phe Pro Lys Phe 35 40 45	
Leu Ser Leu Leu Gly Thr Glu Ile Ile Glu Asn Ala Val Glu Phe Ile 50 55 60	
Leu Arg Ser Met Ser Arg Ser Thr Gly Phe Met Glu Phe Asp Asp Asn 65 70 75 80	
Glu Gly Lys His Ser Ser Lys 85	

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<211> 225

<212> DNA

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	act		ctc	acc						Tyr					acc Thr	48
				Ser	cac His				Ala					Thr	acc Thr	96
cag G1n	ctt Leu	gcc Ala 35	Glu	gcc Ala	cag Gln	gag Glu	gtt Val 40	gaa Glu	ccc Pro	cag Gln	gag Glu	gtc Val 45	Ser	999 Gly	tct Ser	144
tcc Ser	ttg Leu 50	ctg Leu	ccc Pro	tca Ser	ctg Leu	tct Ser 55	gcg Ala	tcc Ser	tcg Ser	gac Asp	tca Ser 60	G1u	tct Ser	gga Gly	aca Thr	192
					gaa Glu 70					taa *				•		225
		210> 211> 212> 213>	74 PRT	o sap	oiens	5										,
	</td <td>100></td> <td>384</td> <td></td>	100>	384													
Met 1				Thr 5	Ser	Trp	His	Leu	Ala 10	Tyr	Leu	Ile	Thr	Trp 15	Thr	
Thr	Cys	Leu	Ala 20		His	Leu	Leu	G1n 25		Ala	Phe	Glu	His 30		Thr	
aln	Leu	A1 a 35		Ala	Gln		Val 40		Pro	Gln	G1u	Va1 45		Gly	Ser	
Ser	Leu 50		Pro	Ser	Leu			Ser	Ser	Asp	Ser 60		Ser	Gly	Thr	
/al		Pro	G1u	Gln	G1u 70		Pro	Arg	Glu		55					

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Met Ala Pro Pro Xaa Ala Xaa Arg Ser Pro Met Ser Xaa Xaa Xaa Xaa
 1
ntg ctg ctg ctg ctg ctg ctg agt ctg gcg ctg ctg ggc gcc cgq qcc
                                                                       96
Xaa Leu Leu Leu Leu Leu Ser Leu Ala Leu Leu Gly Ala Arg Ala
             20
                                 25
cgc gcc gag ccc gcc ggg agt gcc gtc ccc gcg cag agc cgc cca tgc
                                                                      144
Arg Ala Glu Pro Ala Gly Ser Ala Val Pro Ala Gln Ser Arg Pro Cys
         35
                             40
gtg gac tgc cac gcc ttc gag ttc atg cag cgc gcc ctg cag gac ctg
                                                                      192
Val Asp Cys His Ala Phe Glu Phe Met Gln Arg Ala Leu Gln Asp Leu
     50
                         55
cgg aag aca gcc tgc agc ctg gac gcg cgg acg gag acc cta ctg ctg
                                                                      240
Arg Lys Thr Ala Cys Ser Leu Asp Ala Arg Thr Glu Thr Leu Leu Leu
 65
                     70
cag gca gag cgc cgt gcc ctg tgt gcc tgc tgg cca gcg ggg cac tga
                                                                      288
Gln Ala Glu Arg Arg Ala Leu Cys Ala Cys Trp Pro Ala Gly His *
                 85
                                     90
                                                         95
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<210> 386

<211> 95

<212> PRT

<213> Homo sapiens

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		ZZ3~	Xaa	- A	ily A	IIITIO	ACT	u								
Met 1			386 Pro		Ala	Xaa	Arg	Ser	Pro 10	Met	Ser	Xaa	Xaa	Xaa 15	Xaa	
Xaa	Leu	Leu	Leu 20	Leu	Leu	Leu	Ser	Leu 25	Ala	Leu	Leu	Gly	A1a 30		Ala	
Arg	Ala	G1u 35		Ala	Gly	Ser	Ala 40		Pro	Ala	Gln	Ser 45	Arg	Pro	Cys	
Val	Asp 50	Cys	His	Ala	Phe	G1u 55	Phe	Met	G1n	Arg	A1a 60	Leu	Gln	Asp	Leu	
Arg 65	Lys	Thr	Ala	Cys	Ser 70	Leu	Asp	Ala	Arg	Thr 75	Glu	Thr	Leu	Leu	Leu 80	
Gln	Ala	Glu	Arg	Arg 85	Ala	Leu	Cys	Ala	Cys 90	Trp	Pro	Ala	Gly	His 95		
		210> 211> 212> 213>	351	o sap	oiens	5										
	<'	220> 221> 222>	CDS (1)	(3	351)											
	aag		ctc										ctt Leu			48
													aga Arg 30			96
													aaa Lys			144
													gac Asp			192

	50					55					60					
	Arg					Arg					Pro				act Thr 80	240
			gca Ala													288
			gaa Glu 100						Thr							336
	ctt Leu		tgg Trp	tga *												351
	<2 <2	210> 211> 212> 213>	116	sap	oiens	5										
Met 1		400> Gly	388 Leu	Arg 5	Ser	Leu	Ala	Ala	Thr 10	Thr	Leu	Ala	Leu	Phe 15	Leu	
	Phe	Val	Phe 20	-	Gly	Asn	Ser	Ser 25		Ala	Pro	G1n	Arg 30		Leu	
Glu	Arg	Arg 35	Asn	Trp	Thr	Pro	G1n 40		Met	Leu	Tyr	Leu 45		Gly	Ala	
Gln	Gly 50	Arg	Arg	Phe	Ile	Ser 55	Asp	Gln	Ser	Arg	Arg 60	Lys	Asp	Leu	Ser	
Asp 65	Arg	Pro	Leu	Pro	G1u 70	Arg	Arg	Ser	Pro	Asn 75	Pro	Gln	Leu	Leu	Thr 80	
He	Pro	Glu	Ala	A1a 85	Thr	He	Leu	Leu	Ala 90	Ser	Leu	Gln	Lys	Ser 95		
	Asp Leu		Glu 100 Trp	Lys	Asn	Phe	Asp	G1n 105	Thr	Arg	Phe	Leu	G1u 110		Ser	
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<400> 390

Met Asn Leu Gly Val Ser Met Leu Arg Ile Leu Phe Leu Leu Asp Val

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Asp	Phe	Lys 35	Tyr	Ala	Leu	Ile	Gly 40	Thr	· Ala	val	Gly	Va1 45	Ala	Πe	Ser	
Ala	Gly 50	Phe	Leu	Ala	Leu	Lys 55	Ile	Cys	Met	: Ile	Arg 60	Arg	His	Leu	Phe	
Asp 65	Asp	Asp	Ser	Ser	Asp 70	Leu	Lys	Ser	Thr	Pro 75	Gly	Gly	Leu	Ser	Asp 80	
Thr	Ile	Pro	Leu	Lys 85	Lys	Arg	Ala	Pro	Arg 90	Arg	Asn	His	Asn	Phe 95	Ser	
Lys	Arg	Asp	Ala 100	Gln	Val	Ile	Glu	Leu 105								
	<2 <2	211> 212>	391 150 DNA Homo	o saj	piens	S										
	<2		CDS	(150)											
	<2	222>	miso (1) n =	(:	L5O)											
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ggc Gly	ccc Pro	cac His	ccc Pro 20	ctg Leu	gtc Val	cac His	atc Ile	act Thr 25	gag Glu	gaa Glu	gta Val	gaa Glu	gaa Glu 30	aac Asn	agg Arg	96
aca Thr	caa G1n	gat Asp 35	ggc Gly	aag Lys	cct Pro	gag Glu	aga Arg 40	att Ile	gcc Ala	cag G1n	ctg Leu	acc Thr 45	tgg Trp	aat Asn	gag Glu	144
JCC															•	150

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Gly Pro His Pro Leu Val His Ile Thr Glu Glu Val Glu Asn Arg
                                 25
Thr Gln Asp Gly Lys Pro Glu Arg Ile Ala Gln Leu Thr Trp Asn Glu
                             40
Ala
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      <211> 294
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      <220>
      <221> CDS
      <222> (1)...(294)
      <400> 393
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                                                                       48
Met Asp Pro Glu Val Thr Leu Leu Gln Cys Pro Gly Gly Gly Leu
 1
                 5
ccc cag gag cag ata cag gcc gag ctg agc ccc gcc cat gac cgt cgc
                                                                      96
Pro Gln Glu Gln Ile Gln Ala Glu Leu Ser Pro Ala His Asp Arg Arg
             20
                                                     30
cca ctg cca ggt ggg gac gag gcc atc act gcc atc tgg gag acc cgg
                                                                     144
Pro Leu Pro Gly Gly Asp Glu Ala Ile Thr Ala Ile Trp Glu Thr Arg
         35
                                                 45
cta aag gcc caa ccc tgg ctc ttc gac gcc ccc aag ttc cgc ctg cac
                                                                     192
```

Leu Lys Ala Gln Pro Trp Leu Phe Asp Ala Pro Lys Phe Arg Leu His 50 55 tca gcc acc ctg gcg cct att ggc tct cgg ggg cca cag ctg ctc ctg 240 Ser Ala Thr Leu Ala Pro Ile Gly Ser Arg Gly Pro Gln Leu Leu 65 70 75 cgc ctg ggc ctt act tcc tgc cga gtt cta tgt cca gtg cag cct gac 288 Arg Leu Gly Leu Thr Ser Cys Arg Val Leu Cys Pro Val Gln Pro Asp 85 95 ttc tga 294 Phe *

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<400> 394

 Met
 Asp
 Pro
 Glu
 Val
 Thr
 Leu
 Leu
 Leu
 Gln
 Cys
 Pro
 Gly
 Gly
 Gly
 Leu

 Pro
 Gln
 Glu
 Gln
 Ile
 Gln
 Ala
 Glu
 Leu
 Ser
 Pro
 Ala
 His
 Asp
 Arg
 Arg

 Pro
 Leu
 Pro
 Gly
 Gly
 Asp
 Glu
 Ala
 Ile
 Thr
 Ala
 Ile
 Trp
 Glu
 Thr
 Arg

 Leu
 Lys
 Ala
 Gln
 Pro
 Trp
 Leu
 Phe
 Asp
 Ala
 Pro
 Leu
 His

 50
 55
 55
 60
 60
 60
 60
 60

 Ser
 Ala
 Thr
 Leu
 Ala
 Pro
 Ile
 Gly
 Ser
 Arg
 Gly
 Pro
 Gln
 Leu
 Leu

 Ser
 Ala
 Thr
 Ser
 Cys
 Arg
 Val
 Leu</t

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Lys Asn Leu Glu Asn His Gln Phe Pro Ala Lys Pro Leu Arg Glu Ser
    50
                        55
 Gln Ser His Leu Leu Thr Asp Ser Gln Ser Trp Thr Glu Ser Ser Ile
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Asn Pro Gly Lys Cys Lys Ala Gly Met Ser Asn Pro Ala Leu Thr Met
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Glu Asn Glu Thr
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48
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 1
                5
                                   10
                                                      15
ctc cga gcc ctg tcc atc ttc tcc ctg ttg gcc aac atc acc atg ctg
                                                                   96
Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu
            20
gtc agc ttg gtc atg atc tac cag ttc att gtt cag atc ctg tga
                                                                  141
Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu *
         35
                                               45
      <210> 398
      <211> 46
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Met Leu Ser Phe Leu Pro Phe Leu Val Leu Leu Val Phe Ile Arg Asn
                5
                                  10
Leu Arg Ala Leu Ser Ile Phe Ser Leu Leu Ala Asn Ile Thr Met Leu
Val Ser Leu Val Met Ile Tyr Gln Phe Ile Val Gln Ile Leu
                          40
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				Glu				cct Pro 25								96
								gcc Ala								144
								agc Ser								192
ggc Gly 65	aga Arg	tct Ser	cct Pro	atg Met	caa Gln 70	gcc Ala	gtg Val	cat His	cct Pro	gta Val 75	cac His	gtc Val	aaa Lys	gaa Glu	gag Glu 80	240
								ggg Gly								288
gcc Ala	aac Asn	cac His	agt Ser 100	cca Pro	gat Asp	ttt Phe	gac Asp	cat His 105	gac Asp	aga Arg	gat Asp	tac Tyr	gaa Glu 110	gat Asp	gaa Glu	336
		aac Asn 115		-	_		tga *									360

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 Ala Ser Met Ala Glu Asn Ser Ile Pro Leu Tyr Thr Thr Ala Ser Met
 Gly Asn Pro Thr Leu Gly Asn Leu Ala Ser Ala Ile Arg Glu Glu Leu
                             40
 Asn Gly Ala Met Glu His Thr Asn Ser Asn Glu Ser Asp Ser Ser Pro
                         55
                                             60
 Gly Arg Ser Pro Met Gln Ala Val His Pro Val His Val Lys Glu Glu
                     70
                                         75
 Pro Leu Asp Pro Glu Glu Ala Glu Gly Pro Leu Ser Leu Val Thr Thr
                                     90
 Ala Asn His Ser Pro Asp Phe Asp His Asp Arg Asp Tyr Glu Asp Glu
            100
                                 105
 Pro Val Asn Glu Asp Met Glu
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      <211> 474
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                                                                       48
Met Ser Lys Ser Cys Gly Asn Asn Leu Ala Ala Ile Ser Val Gly Ile
                 5
                                                          15
tcg ctt ctt tta ctc tta gtg gtt tgt gga att ggg tgt gtt tgg cac
                                                                       96
Ser Leu Leu Leu Leu Val Val Cys Gly Ile Gly Cys Val Trp His
             20
                                                      30
tgg aaa cac cgt gtt gcc aca cga ttt acc tta ccg agg ttt tta caa
                                                                      144
Trp Lys His Arg Val Ala Thr Arg Phe Thr Leu Pro Arg Phe Leu Gln
                             40
                                                 45
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agg Arg	aga Arg 50	Ser	agc Ser	agg Arg	aga Arg	aaa Lys 55	Val	tgt Cys	act Thr	: aaa · Lys	aca Thr	Phe	ttg Lei	ggo Gly	ccc Pro		192
cgc Arg 65	Ile	att Ile	ggc Gly	tta Leu	agg Arg 70	cat His	gaa Glu	atc Ile	tca Ser	gtt Val 75	Glu	acc Thr	caa Gln	gac Asp	cac His 80		240
aaa Lys	tct Ser	gct Ala	gtc Val	agg Arg 85	gga Gly	aat Asn	aac Asn	aca Thr	cac His 90	Asp	aac Asn	tat Tyr	gaa Glu	aat Asn 95			288
gaa Glu	gca Ala	ggt Gly	cct Pro 100	ccc Pro	aaa Lys	gct Ala	aaa Lys	gga Gly 105	aaa Lys	acc Thr	gat Asp	aag Lys	gaa Glu 110	cta Leu	tat Tyr		336
gaa Glu	aac Asn	aca Thr 115	ggg Gly	cag Gln	tct Ser	aat Asn	ttc Phe 120	gag Glu	gag Glu	cat His	atc Ile	tat Tyr 125	gga Gly	aat Asn	gag Glu		384
aca Thr	tct Ser 130	tct Ser	gac Asp	tat Tyr	tat Tyr	aac Asn 135	ttc Phe	cag Gln	aag Lys	cct Pro	cgt Arg 140	cct Pro	tct Ser	gaa Glu	gtt Val	*.	432
					ata Ile 150								tag *				474
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	<2	?11>	157														
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Ser	Leu		Leu 20	Leu	Leu	Val				Ile	Gly	Cys	Va1 30	Trp	His		
Trp				Val.	A1a				Thr	Leu	Pro	Arg 45		Leu	Gln		
Arg			Ser .	Arg ,				Cys	Thr		Thr 60		Leu	Gly	Pro		

Arg 65	Πe	e Ile	e Gly	' Leu	Arg	His	Glu	Ile	Ser	Val 75	Glu	Thr	Gln	Asp	His 80	
Lys	Ser	· Alā	a Val	Arg 85	Gly	Asn	ı Asn	Thr	His 90	Asp	Asn	Tyr	Glu	Asn 95	Val	
Glu	Ala	Gly	Pro 100		Lys	Ala	Lys	Gly 105		Thr	Asp	Lys	Glu 110		Tyr	
Glu	Asn	Thr 115	Gly	Gln	Ser	Asn	Phe 120		Glu	His	Ile	Tyr 125	Gly		Glu	
	130		· Asp			135					140		Ser	Glu	Val	
Pro 145	Gln	Asp	Glu	Asp	Ile 150		Ile	Leu	Pro	Asp 155		Tyr				
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			gtg Val												Val	48
			gtt Val 20													96
tgg Trp	ttc Phe	atc Ile 35	agg Arg	gga Gly	aag Lys	gac Asp	ccc Pro 40	cag Gln	ccc Pro	gtg Val	gag Glu	gag Glu 45	gaa Glu	aag Lys	agc Ser	144
			cgc Arg													192
gac Asp 65			cag Gln													240
aaa	gct	gtg	ctg	aac	aga	aac	cgc	сса	gag	aag	aat	taa				279

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 Phe Trp Thr Val
 Val
 Arg Thr Tyr Ala
 Pro Tyr Val
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 Thr Phe Pro Val
 Ala Phe Val
 Val
 Gly
 Ala Val
 Gly
 Tyr His Leu
 Glu

 Trp Phe Ile Arg Gly
 Lys
 Asp Pro Gln
 Pro Val
 Glu
 Glu
 Glu
 Lys
 Ser

 35
 40
 45
 45

 Ile Ser Glu
 Arg Arg
 Glu
 Asp Arg
 Lys
 Leu
 Asp Glu
 Leu
 Leu
 Gly
 Lys

 Asp His Thr Gln
 Val
 Val
 Ser
 Leu
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 Asp Lys
 Leu
 Glu
 Phe Ala
 Pro

 65
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 Lys
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 Pro
 Glu
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90

cag cct aaa agg cga cgg cgg att gac aga agt atg att gga gag ccc Gln Pro Lys Arg Arg Arg Arg Ile Asp Arg Ser Met Ile Gly Glu Pro 20 25 30

aca aac ttt gtg cat aca gct cat gtt gga tca gga gac ctg ttc agt
Thr Asn Phe Val His Thr Ala His Val Gly Ser Gly Asp Leu Phe Ser
35 40 45

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48

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			ggt Gly													240
			gga Gly	tag *												255
	<; <;	211> 212>	406 84 PRT Homo	sap	oiens	ŝ										
		100>		_		_										
Met 1	Ser	Glu	Phe	Trp 5	Leu	Cys	Phe	Asn	Cys 10	Cys	Ile	Ala	Glu	G]n 15	Pro	
Gln	Pro	Lys	Arg 20	Arg	Arg	Arg	Пe	Asp 25		Ser	Met	Пе	Gly 30		Pro	
Thr	Asn	Phe 35	Val	His	Thr	Ala	His 40	Val	Gly	Ser	Gly	Asp 45	Leu	Phe	Ser	
Gly	Met 50		Ser	Val	Ser	Ser 55	Пe	Gln	Asn	Gln	Met 60		Ser	Lys	Gly	
Gly 65		Gly	Gly	Gly	Met 70		Ala	Asn	Val	G1n 75	~ ~	Gln	Leu	۷a٦	Asp 80	
Thr	Lys	Ala	Gly													
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Met 1	Ala	Ser	Ser	Gly 5	Gly	Ala	Gly	Ala	Ala 10	Ala	Ala	Ala	Ala	Ala 15	Ala	
	ctg Leu															96
	att Ile															144
	ctt Leu 50															192
	gag G1u															240
	agc Ser	tga *														249

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<211> 82

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 Met
 Ala
 Ser
 Ser
 Gly
 Gly
 Ala
 Gly
 Ala
 A

Thr Ser

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 1
                  5
                                      10
ctc ctg ggt gct gcc aca gag aag aga gag aga gtg aag cgg gca gag
                                                                        96
Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
             20
act ggc tgt tgc cat cac aca act gag ggc gga cct gga gct cac cgg
                                                                       144
Thr Gly Cys Cys His His Thr Thr Glu Gly Gly Pro Gly Ala His Arg
         35
                              40
ctg agg gtt tga
                                                                       156
Leu Arg Val *
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                                    10
Leu Leu Gly Ala Ala Thr Glu Lys Arg Glu Arg Val Lys Arg Ala Glu
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Thr Gly Cys Cys His His Thr Thr Glu Gly Gly Pro Gly Ala His Arg
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Leu Arg Val
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acc Thr	ctg	gct Alá	cag a Glr 20	ı Ala	gag Glu	gag Glu	cag Gln	cag Gln 25	Pro	tac Tyr	cto Leu	gag Glu	ggc Gly 30	Ser	acc Thr	96
gtt Val	atg Met	cgc Arg 35	Gly	act Thr	cgc Arg	tgt Cys	ctg Leu 40	Ala	gag Glu	tac Tyr	cac His	ctg Leu 45	Gly	gat Asp	tat Tyr	144
gga Gly	cac His 50	Ala	tgg Trp	aac Asn	agg Arg	tgt Cys 55	tgg Trp	gtg Val	ctg Leu	gac Asp	agg Arg 60	gtg Val	gac Asp	acc Thr	tgg Trp	192
gct Ala 65	Val	gtc Val	atg Met	ttc Phe	att Ile 70	gat Asp	ttt Phe	gga Gly	cag Gln	ttg Leu 75	gcc Ala	acc Thr	atc Ile	cct Pro	gtg Val 80	240
cag Gln	tct Ser	ctg Leu	cgc Arg	anc Xaa 85	tna Xaa	gac Asp	agc Ser	gac Asp	gac Asp 90	ttc Phe	tgg Trp	acc Thr	atc Ile	cca Pro 95	ccc Pro	288
ctg Leu	act Thr	cag Gln	cca Pro 100	ttc Phe	atg Met	ctg Leu	gag Glu	aaa Lys 105	gac Asp	att Ile	ttg Leu	agt Ser	tcg Ser 110	tat Tyr	gag Glu	336
gtt Val	gtc Val	cat His 115	cga Arg	atc Ile	ctc Leu	Lys	999 Gly 120	aaa Lys	atc Ile	act Thr	ggt Gly	gct Ala 125	ttg Leu	aac Asn	tcg Ser	384
gcg	ttg	cac	atc	cta	aag	ttt	gaa	gag	tct	aaa	taa					420

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                            40
Gly His Ala Trp Asn Arg Cys Trp Val Leu Asp Arg Val Asp Thr Trp
Ala Val Val Met Phe Ile Asp Phe Gly Gln Leu Ala Thr Ile Pro Val
                    70
                                        75
Gln Ser Leu Arg Xaa Xaa Asp Ser Asp Asp Phe Trp Thr Ile Pro Pro
                                    90
Leu Thr Gln Pro Phe Met Leu Glu Lys Asp Ile Leu Ser Ser Tyr Glu
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	cto Lei	c ct u Le	a at u Me	et P	ca ro 20	gca Ala	gta Va	a tc I Se	t gt r Va	t gg 1 Gl: 2!	y Ası	t gt n Va	t gg 1 G1	c caq y Glr	g ct 1 Lei 30	u Al	a atg a Met	96
	gat Asp	ct _e	ı Il	t a e I 85	tt le	tct Ser	aca Thr	ctg	aat Asr 4(n Met	g to t Ser	t aag ^ Lys	at Ile	t ggt e Gly 45	/ Tyr	c tt r Ph	c tat e Tyr	144
	acc Thr	gat Asp 50	э Су	t c s L	tt eu	gtg Val	cca Pro	ato Met 55	: Val	gga Gly	a aad ⁄ Asr	aat Asr	cca Pro 60) Tyr	: gcg	aco Thi	c aca r Thr	192
	gaa Glu 65	Gly	a aa ⁄ As	t to n Se	ca er	aca Thr	gaa Glu 70	Leu	ago Ser	ata Ile	aat Asn	gct Ala 75	Glu	a gtg ı Val	tat Tyr	tca Ser	ttg Leu 80	240
	cct Pro	tca Ser	ag Arg	a aa g Ly	ag /s	ctg Leu 85	gtg Val	gct Ala	cta Leu	cag G1n	tta Leu 90	Arg	tcc Ser	att Ile	ttt Phe	att Ile 95	aag Lys	288
	tat Tyr	aaa Lys	tca Ser	a aa Ly 10	'S	cca Pro	ttc Phe	tgt Cys	gaa Glu	aaa Lys 105	ctg Leu	ctt Leu	tcc Ser	tgg Trp	gtg Val 110	aaa Lys	agc Ser	336
	agt Ser	ggc Gly	tgt Cys 115	A1	c a a A	aga Arg	gtc Val	att Ile	gtt Val 120	ctt Leu	tca Ser	agc Ser	agt Ser	cat His 125	tca Ser	tat Tyr	cag G1n	384
	cgt Arg	aat Asn 130	gat Asp	ct Le	g d u G	cag Gln	ctt Leu	cgt Arg 135	agt Ser	act Thr	ccc Pro	ttc Phe	cgg Arg 140	tac Tyr	cta Leu	ctt Leu	aca Thr	432
	cct Pro 145	tcc Ser	atg Met	ca: Gli	aa n L	.ys :	agt Ser 150	gtt Val	caa Gìn	aat Asn	aaa Lys	ata Ile 155	aag Lys	agc Ser	ctt Leu	aac Asn	tgg Trp 160	480
(gaa Glu	gaa Glu	atg Met	gaa Glu	ı L	aa a ys S 65	agc Ser	cgg Arg	tgc Cys	He	cct Pro 170	gaa Glu	ata Ile	gat Asp	gat Asp	tcc Ser 175	gag Glu	528

ttt t Phe C	igt at Cys Il	c cg e Ar 18	g Ile	t ccq e Pro	g gga o Gly	gga Gly	a gg / Gly 189	/ I](c ac e Th	a aa r Ly	a ac s Th	a ct r Le 19	u Ty	t gat r Asp	576
gaa a Glu S	igc tg Ser Cy 19	s Se	t aaa r Lys	a gaa Glu	atc Ile	Caa Glr 200) Met	g gca : Ala	a gt a Va	t cte	g ct u Le 20	u Ly	a tt s Ph	t gtt e Val	624
tca g Ser G 2	aa gg lu Gl 10	g gad y Asp	c aac o Asr	ato Ile	cca Pro 215	gat Asp	gcā Ala	tta Leu	a ggt I Gly	t cti y Lei 220	ı Va	t gag	g ta u Tyı	t ctt r Leu	672
aat g Asn G 225	ag tg lu Tr	g ctt p Leu	cag u Gln	ata Ile 230	ctc Leu	aaa Lys	ccą Pro	ctt Leu	ago Ser 235	· Asp	gad Asp	cco Pro	c aca	gta Val 240	720
tct go Ser A	cc tca la Sen	a cgg r Arg	tgg Trp 245	Lys	ata Ile	cca Pro	agt Ser	tct Ser 250	Trp	g aga Arg	tta Lei	cto Lei	ttt Phe 255	Gly	768
agt go Ser Gl	gt cti ly Lei	ccc Pro 260	Pro	gca Ala	ctt Leu	ttc Phe	tga *								795
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Asp Le	u Ile 35	Пе	Ser	Thr		Asn 40		Ser	Lys	Ile	Gly 45	Tyr	Phe	Tyr	
Thr Asp 50	p Cys	Leu	Val				Gly	Asn	Asn	Pro 60		Ala	Thr	Thr	
Glu Gly 65				G1u 70	Leu S				75	Glu				80	
Pro Sei	r Arg	Lys			Ala I	_eu	G1n	Leu 90	Arg	Ser	Пе	Phe	I 1e 95	Lys	
Tyr Lys	s Ser	Lys	Pro	Phe	Cys (alu	Lys	Leu	Leu	Ser	Trp	Va1	Lys	Ser	

			100					105					110			
Ser	Gly	Cys 115		Arg	Val	Ile	Val 120		Ser	Ser	Ser	His 125		Tyr	Gln	
Arg	Asn 130		Leu	Gln	Leu	Arg 135		Thr	Pro	Phe	Arg 140	Tyr		Leu	Thr	
Pro 145	Ser	Met	Gln	Lys	Ser 150	Val	Gln	Asn	Lys	Ile 155	Lys	Ser	Leu	Asn	Trp 160	
				165					170		Ile			175	Glu	
			180					185			Lys		190		•	
		195					200				Leu	205	-	·		
	210					215					Leu 220					
225					230					235	Asp				240	
				245				Ser	Ser 250	Trp	Arg	Leu	Leu	Phe 255	Gly	
Ser	Gly	Leu	Pro 260	Pro	Ala	Leu	Phe									
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gag Glu	ctc Leu	tta Leu	aaa Lys 20	gca Ala	gag Glu	acg Thr	ctt Leu	tcc Ser 25	cag Gln	ctt Leu	999 Gly	tca Ser	gag Glu 30	aga	ttc Phe	96
atc Ile	atg Met	aga Arg <i>i</i> 35	aga Arg :	tct (Ser	cca Pro	cta Leu	gct Ala 40	gtt Val	gct Ala	gga Gly	ttt Phe	cag Gln 45	gat Asp	gga Gly	gga Gly	144

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aga ctc aag cag aga gac ctg gtg gcc act aga agc ttg gaa cag ccc
                                                                        192
 Arg Leu Lys Gln Arg Asp Leu Val Ala Thr Arg Ser Leu Glu Gln Pro
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                                               60
 tca gtt gat agc aag gaa atg agg act cag tga
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 Ser Val Asp Ser Lys Glu Met Arg Thr Gln *
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Arg Leu Lys Gln Arg Asp Leu Val Ala Thr Arg Ser Leu Glu Gln Pro
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Ser Val Asp Ser Lys Glu Met Arg Thr Gln
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 1
                                     10
cag cta tta atg tca tgt ccc caa gtt gaa tta att cag tgt ctc act
                                                                       96
Gln Leu Leu Met Ser Cys Pro Gln Val Glu Leu Ile Gln Cys Leu Thr
             20
                                 25
                                                     30
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aaa Lys	a gag s Glu	ttq Leu 35	ı Asr	gaç 1 Gli	g aaa Lys	a caa Glr	CC6 Pro 40) Ser	tta Leu	tci Ser	t tti Phe	t ggt e Gly 45	/ Lei	t gct u Ala	ata Ile	144
cti Lei	cat u His 50	Lei	tto Phe	tct Ser	gca Ala	gac Asp 55	Met	aaa : Lys	aaa Lys	ıgtt Val	ggd Gly 60	/ I]e	aag Lys	g cta S Leu	ctt Leu	192
caa G1r 65	ı Glu	ato Ile	: aat : Asn	aaa Lys	ggt Gly 70	Gly	ata Ile	gat Asp	gca Ala	gta Val 75	G٦٤	agt Ser	ctt Leu	atg Met	ata Ile 80	240
aat Asr	gat Asp	tcc Ser	ttt Phe	tgc Cys 85	Ser	ata Ile	gaa Glu	aag Lys	tgg Trp 90	caa Gln	gaa Glu	gtg Val	gca Ala	aat Asn 95	ata Ile	288
tgt Cys	tca Ser	cag G1n	aat Asn 100	ggc Gly	ttt Phe	gac Asp	aaa Lys	tta Leu 105	tct Ser	aat Asn	gac Asp	atc Ile	acg Thr 110	Ser	att Ile	336
ctt Leu	cga Arg	tct Ser 115	Gln	gct Ala	gca Ala	gtt Val	aca Thr 120	gaa Glu	att Ile	tct Ser	gaa Glu	gag Glu 125	Asp	gac Asp	gca Ala	384
						gtg Val 135				<u> </u>						414
	<'a	211> 212>		sar	oiens	5										
Mat		100>		۰۵	07				ъ.							
Met 1	GIU	ıyr	116	5 5	Gin	Leu	Lys	Asp	Phe 10	Ihr	lhr	Asp	Asp	Leu 15	Leu	
Gln	Leu	Leu	Met 20	Ser	Cys	Pro	Gln	Va1 25	Glu	Leu	Ile	G1n	Cys 30	Leu	Thr	
Lys	Glu	Leu 35	Asn	Glu	Lys	Gln	Pro 40		Leu	Ser	Phe	Gly 45		Ala	Ile	
Leu	His 50		Phe	Ser	Ala	Asp 55		Lys	Lys	Val	Gly 60		Lys	Leu	Leu	
Gln		Пе	Asn	Lys	Gly	Gly	Ile	Asp	Ala	Val		Ser	Leu	Met	Пе	

65					70					75					80	
				85					90	o Gli	n Glu			95	ılle	
			100)				105	5				110	Ser	. Ile	
Leu	Arg	Ser 115	Glr	ı Ala	ı Ala	a Val	Thr 120		ı 176	Sei	r Glu	u G1u 125		Asp	Ala	
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cgt Arg	gat Asp	gtt Val	cat His 20	ttt Phe	ggt Gly	ttt Phe	cta Leu	agc Ser 25	gag Glu	agg Arg	ctc Leu	cga Arg	gcc Ala 30	ttc Phe	caa Gln	96
cct Pro	ctg Leu	act Thr 35	ggc Gly	tgg Trp	tcc Ser	tgt Cys	gag Glu 40	acc Thr	cct Pro	cga Arg	tca Ser	ggg Gly 45	atg Met	ctg Leu	ctg Leu	144
caa Gln	gtg Val 50	gtc Val	atg Met	gca Ala	gtt Val	gct Ala 55	gac Asp	acc Thr	tct Ser	gcg Ala	aag Lys 60	gcc Ala	gtg Val	gag Glu	acc Thr	192
gtg /al 65	aag Lys	aag Lys	cag Gln	caa G1n	ggc Gly 70	gag Glu	cag Gln	atc Ile	tgc Cys	tgg Trp 75	ggt Gly	ggc Gly	agc Ser	agc Ser	tcc Ser 80	240
itc a 'al N	atg 1et :	agt Ser	cta Leu	gct Ala 85	acc Thr	aag Lys	atg Met	aat Asn	gaa Glu 90	cta Leu	atg Met	gag Glu	aaa Lys	tag *		285

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	, Asp	Va [*]	1 His 20		e Gly	/ Phe	. Lei	ı Ser 25		ı Arç	J Leu	ı Arç	A1a 30	15 a Phe	e Gln		
Pro	Let	Thi		/ Trp) Ser	Cys	G1t 40	_	Pro	Arç	, Ser	· Gly 45		: Lei	ı Leu		
G1r	Va1 50	Val	l Met	: Ala	a Val	A1 a 55	Asp) Thr	`Ser	Ala	Lys 60		va1	G1ı	Thr		
65					7.0					75					Ser 80		
۷a٦	Met	Ser	. Leu	A1 a 85	Thr	Lys	Met	: Asn	G1u 90	Leu	Met	. Glu	Lys	;			
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tgg Trp	gtg Val	tgc Cys	tgg Trp 20	gag Glu	cca Pro	999 Gly	atc Ile	act Thr 25	ggg Gly	tgc Cys	cgg Arg	cca Pro	cag G1n 30	Arg	aag Lys		96
gtc Val	cct Pro	gag Glu 35	gac Asp	aca Thr	gta Val	ccg Pro	aag Lys 40	tct Ser	gat Asp	ccc Pro	aga Arg	gga Gly 45	gga Gly	agg Arg	aag Lys	1	.44
gtg Val	ggc Gly	cgg Arg	gga Gly	gaa G1u	ggt Glv	ctg Leu	agt Ser	gca Ala	999 Glv	atg Met	gtc Val	cag Gln	gag Glu	gag Glu	gac Asn	1	92

50

55

60

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Val Gly Arg Gly Glu Gly Leu Ser Ala Gly Met Val Gln Glu Glu Asp

Trp Lys Leu Gln Asp Gly Cys Arg Gly Pro Trp Thr Leu Leu Ala

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